RADIOACTIVE IODINE IN THE DIAGNOSIS OF THYROID DISEASE

BY

BENGT SKANSE

UPPSALA 1949
ALMQVIST & WIKSELLS BOKTRYCKERI AB

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MED. LIC., VÄRML.

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To my wife

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PREFACE

The present investigation was carried out in the period 1946—1948 in Boston, Mass., during the tenure of a Rockefeller Fellowship (1946—1947) and a Henry P. Walcott Fellowship of Harvard University (1947—1948).

Dr. Jan Waldenström, Professor of Theoretical Medicine at the University of Upsala, suggested the problem and arranged for my going to the United States. I am greatly indebted to him for thus initiating my studies, for valuable suggestions and criticism during the preparation of the manuscript after my return home, and for his constant personal interest and invaluable support.

At the Massachusetts General Hospital preliminary studies concerning the use of radioactive iodine for diagnostic purposes had been started before my arrival. I was given the opportunity to continue these studies, directed primarily to the use of radioactive iodine in evaluating thyroid function.

It is my pleasant duty to express my sincere gratitude to Dr. J. H. Means, Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services of the Massachusetts General Hospital, for placing the facilities of his clinic at my disposal. His high example as clinician, investigator, and teacher was a source of daily inspiration. His warm friendliness and uncompromising objectivity contributed greatly to investigative work. With his help it became possible for me to stay a second year in Boston.

My warm thanks are also due to Dr. R. W. Rawson, who was in charge of the Metabolism Laboratory and the Research Laboratory of the Thyroid Clinic. His unfailing energy in arranging the best possible working conditions for me, his scientific enthusiasm, and his encouraging interest contributed greatly to the present investigation.

I had the opportunity to carry out a considerable part of my studies at the Massachusetts Institute of Technology. I should like to thank Dr. R. D. Evans, Professor of Physics and Head of the Radioactivity Center, for providing facilities for me in his laboratory. His extensive knowledge of the applicability of radioactive isotopes to medical problems has been most valuable for my work. I am most obliged to him and to his staff, in particular to Dr. R. G. Fluharty.

The determinations of the serum protein-bound iodine for the Massachusetts General Hospital were performed by Dr. D. S. Riggs of the Department of Pharma-

cology of the Harvard Medical School. It has been most advantageous to have these difficult analyses made by one of the outstanding investigators in that field, and I am greatly indebted to him for placing his material at my disposal. I should also like to extend my thanks to my colleagues at the Massachusetts General Hospital for their personal interest and for valuable discussions. In particular my thanks are due to Drs. B. M. Dobyns, C. E. Richards, T. H. Coleman, E. M. Chapman, W. M. Jefferies, J. W. McArthur, and J. Lerman. I am grateful for the help given by Drs. O. Cope and E. Hamlin, Jr., who were responsible for most of the thyroid surgery.

For helpful discussions, particularly of the statistical treatment of the problem concerning the collection of radioactive iodine by the thyroid, I wish to thank Professor G. Dahlberg, Head of the Swedish State Institute of Human Genetics and Race Biology. My thanks are also due to Mrs. E. Tibbling at the same institute who assisted with the statistical calculations.

Professor E. Bárány has given me valuable support both during his stay in Boston and after my return home. His encouragement and critical suggestions have been of great help for which I am deeply grateful.

The revision of the English text was most competently carried out by Dr. and Mrs. R. L. Berg of Boston, Mass. They also have undertaken the painstaking work of drawing the figures. Their untiring support, encouragement, and generousness have been the greatest asset in the preparation of the manuscript.

For technical assistance my acknowledgments are due to Miss L. Kirschner, Miss P. Merrill, Miss B. Lennon, Miss O. Joneson, and Miss A. Guardo at the Massachusetts General Hospital, and Mrs. H. Lockhart and Miss H. Yee at the Massachusetts Institute of Technology.

For financial assistance I am indebted to the Rockefeller Foundation, to Harvard University, to the Swedish Medical Research Council, and to the University of Upsala. Certain laboratory expenses were defrayed by grants from the American Cancer Society through the Growth Committee of the National Research Council, the Loomis Institute for Scientific Research, Inc., and the Parke, Davis & Company.

Last but not least I want to express my gratitude to my wife for her invaluable assistance and cooperation, for her tireless interest, and for her most stimulating encouragement. Certainly this investigation would never have been completed without her help.

Bengt Skanse

ABBREVIATIONS

BMR	= basal metabolic rate
BP	= blood pressure
c	= cool
D	= diffuse
d	= dry
ECG	= electrocardiogram
f	= firm
h	= hard
Hgb	= hemoglobin
KI	= potassium iodide
KSCN	= potassium thiocyanate
m	= moist
N	= nodular
n	= normal
NPN	= nonprotein nitrogen
op.	= operation
PBI	= serum protein-bound iodine
PTU	= propylthiouracil
RBC	= red blood cell count
s	= soft
TSH	= thyrotropic hormone
TU	= thiouracil
U. S. P.	= United States Pharmacopeia
w	= warm

Chapter I

INTRODUCTION

Typical cases of thyrotoxicosis usually do not present diagnostic problems. There is no doubt, however, that thyrotoxicosis may present itself in such forms that even an experienced clinician will have difficulties in making the diagnosis with any certainty.

This is especially true as thyrotoxicosis may simulate a number of other diseases such as cardiovascular disease, anxiety neurosis, and gastro-intestinal disturbances. One or more of the cardinal symptoms may be missing, or the whole clinical picture may be vague and nebulous.

A number of laboratory tests have been devised to aid in the diagnosis of disturbances of thyroid function. Generally such tests estimate the functional state of the thyroid in four ways:

1. The effect of the released hormone on the organism or on some system in the organism.
   a) Basal metabolic rate (BMR)
   b) Serum cholesterol
   c) Leucocyte pattern
   d) Creatine tolerance test
   e) Blood sugar
2. The amount of thyroid hormone released.
   a) Serum protein-bound iodine (PBI)
   b) Total blood or serum iodine
3. The thyroid's need for, or ability to metabolize, some specific substance that is necessary for its function.
   a) Iodine tolerance tests
4. The effect of an interfering substance.
   a) Response to iodine

Figure 1 gives a schematic representation of the way in which the various tests fit into the physiology of the thyroid.

The different tests thus measure various aspects of thyroid function. There is at present no suitable test for measuring thyrotropic hormone, but a rather complete

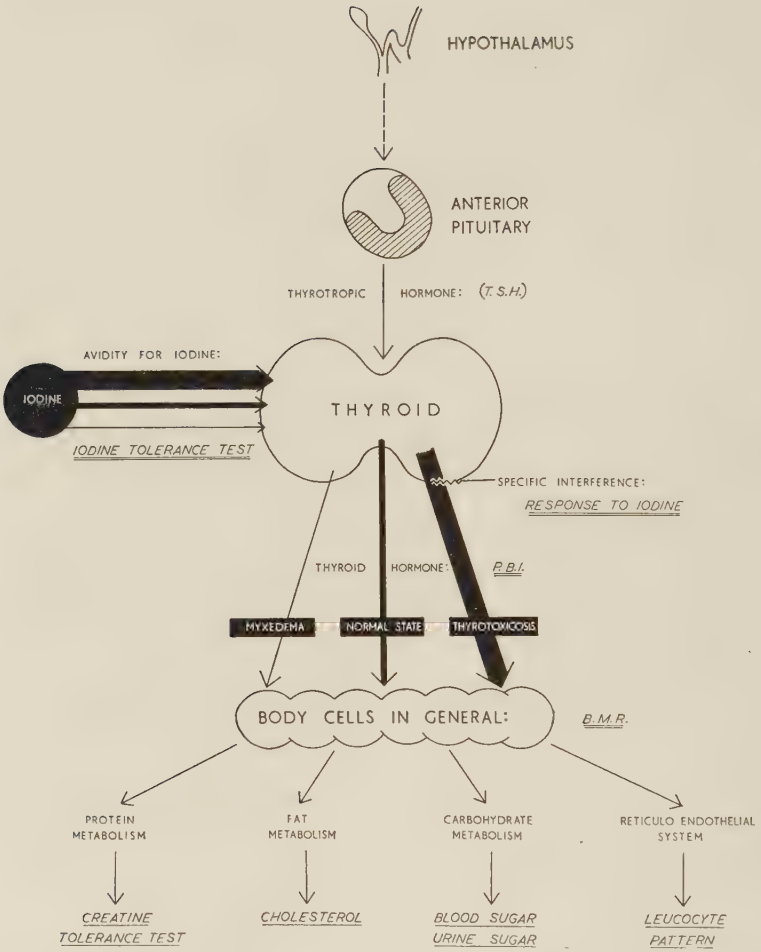

Fig. 1. A schematic representation indicating the relation of the various laboratory tests to the function of the thyroid.

picture of the morbid physiology of a patient with disturbed function of the thyroid could be obtained from a representative test from each of the four groups indicated. Such a complete study of thyroid physiology is neither practical nor necessary in clinical work.

However, there is no single test that is entirely satisfactory. The determination of the basal metabolic rate has been and still is the classical laboratory test in thyrotoxicosis. Though it is true that the majority of patients with thyrotoxicosis present an elevated basal metabolic rate, there are a certain number of patients whose basal metabolic rates stay within normal limits even while thyrotoxic. It is also true that there are a number of extrathyroid causes for elevated basal metabolic rates. Thus, the BMR is not an ideal diagnostic aid. The iodine response test

(Means, 1933) in many respects is a specific and reliable test, but it is somewhat impractical for routine clinical use. More recently the determination of the serum protein-bound iodine has given encouraging results in the diagnosis of thyroid disturbances, but the complicated analytical technique limits its clinical usefulness. There is, therefore, a definite need for a simple, reliable, and specific test for thyrotoxicosis.

The main objective of the present investigation was to ascertain whether a radioactive iodine tolerance test could be worked out as an aid in the diagnosis of thyrotoxicosis. Though a few previous attempts had not been very successful, there were good theoretical reasons to assume that a suitable radioactive iodine tolerance test would be able to register the differences in the functional activity of the thyroid in such a way that it could be used for diagnostic purposes. The development of the test involved methodological problems such as the standardization of the radioactive isotope of iodine in absolute units and the measurement of the radioactive iodine in the thyroid *in situ*. The reliability and specificity of the test then had to be established by means of studies on representative clinical material. To a considerable extent this involved comparison with other laboratory tests, primarily the basal metabolic rate and the serum protein-bound iodine. The serum cholesterol was also considered, although previous studies indicated that it was of limited value. For similar reasons other tests such as the leucocyte pattern and creatine tolerance tests were not dealt with.

As a test the response to iodine has the advantage of clinical simplicity without the necessity for complicated laboratory procedures. However, it has certain disadvantages that limits its value: it requires many careful basal metabolic rate determinations; it involves a long period of observation; it is sometimes difficult to evaluate the response; and finally, there are a certain percentage of thyrotoxic patients that are resistant to iodine treatment. For these reasons it was not feasible to compare it with the radioactive iodine tolerance test.

When it became evident that the radioactive iodine tolerance test would be of diagnostic value, it was necessary to adopt a technique convenient and suitable for use in the clinic. With the use of this technique the radioactive iodine tolerance test can be advantageously used in the evaluation of thyroid function and particularly in the diagnosis of thyrotoxicosis.

Chapter II

REVIEW OF THE LITERATURE DEALING WITH TESTS OF THYROID FUNCTION

Basal Metabolic Rate

During the last three decades the determination of the basal metabolic rate has been extensively used as an aid in the diagnosis of thyrotoxicosis. Its value is well established. For a review of the subject the reader is referred to the monographs by Du Bois (1936) and Eggert Møller (1925, 1927). There is no doubt that the BMR is elevated in most patients with thyrotoxicosis. However, there are two circumstances which decrease the reliability of the test. In the first place, normal BMR's may occur in thyrotoxicosis; and in the second place, there are a number of conditions in which the BMR is elevated in the absence of thyrotoxicosis. These circumstances are of such importance that a brief review of the literature on these points is presented.

The possibility that a normal BMR might be found in occasional mild and atypical cases of thyrotoxicosis was considered as early as 1916 by Du Bois. Beall (1921) found that of 26 patients with clinical thyrotoxicosis the BMR was below +15 per cent in 10 cases. Liebesny and Schwartz (1922) studied 46 patients with thyrotoxicosis of whom 10 had basal metabolic rates below +15 per cent. In 1925 Eggert Møller carefully studied 89 unselected cases of thyrotoxicosis and found that 21 per cent had basal metabolic rates of +10 per cent or below and 31 per cent had basal metabolic rates of +20 per cent or below. As a possible explanation for the combination of normal basal metabolism and thyrotoxicosis Eggert Møller suggested that it was found in individuals whose normal BMR was low, and that the increase in BMR as a result of thyrotoxicosis was not enough to exceed the upper limit of normal.

Jahn (1928) reported a group of 133 cases of thyrotoxicosis of whom 41 per cent had normal and 12 per cent had low BMR's. No normal limits are given, however, and the clinical data are meager. In another series of 127 unselected cases of thyrotoxicosis (Lublin, 1930) there were 36 cases with a normal BMR (between —11 and +12 per cent). Plummer (1931) reported a carefully studied case of thyrotoxicosis with a BMR of —9 per cent where typical symptoms of thyrotoxicosis disappeared following operation.

The problem of normal basal metabolism in thyrotoxicosis was thoroughly studied

by Troell (1932). In about 600 cases of thyrotoxicosis he found 14 cases (about 2 per cent) with a BMR below +20 per cent. His results were supported by convincing case histories, by microscopical examinations of the resected thyroids showing typical hyperplastic goiter in 12 cases, and by good results of thyroidectomies. He advocated that a histological diagnosis should be required for the diagnosis of thyrotoxicosis with normal BMR.

Bram (1933) reviewed 220 cases of thyrotoxicosis with BMR's below +15 per cent. Of these, however, only 74 were definitely untreated, the remaining cases having had some treatment (iodine, subtotal or total thyroidectomy, or X-ray). It is not possible to evaluate how well the diagnoses were established.

In a critical study Gordon and Graham (1935) reported 71 cases of clinical hyperthyroidism with normal BMR (between —10 and +15 per cent). There was a greater than usual preponderance of females (69 cases). The description of the symptomatology indicates that the diagnosis was generally correct. This was further supported by the results of thyroidectomy, following which 63 per cent were cured and 23 per cent improved. Their study indicated that this syndrome exists more commonly in the presence of nodular goiter (54 cases) than diffuse goiter (17 cases). They concluded that the diagnosis of thyrotoxicosis in the presence of a normal BMR should not be made until a thorough investigation had failed to reveal any other organic or psychological basis for the patient's illness.

Sixty cases of thyrotoxicosis with BMR's between —37 and +12 per cent were reported by Davison (1937). Following subtotal thyroidectomy 56 patients were cured and four improved. Davison was of the opinion that normal BMR's appeared mainly in patients with long-standing disease.

In 1938 Hendrick reported on 47 cases of thyrotoxicosis with basal metabolic rates between —26 and +13 per cent. All patients had goiters. Thyroidectomy was performed in all cases and the results were considered good. He warned against relying too heavily on the basal metabolism for the diagnosis of thyrotoxicosis. Anderson (1941) found the BMR below +15 per cent in six of 107 patients with frank hyperthyroidism and in 12 of 42 patients with clinically borderline hyperthyroidism but with goiter and two or three of the following symptoms: tremor, tachycardia, sweating, weight loss. In 194 unselected cases of thyrotoxicosis Bergenfeldt (1942) observed 15 patients (7.7 per cent) with a BMR below +15 per cent and nine patients with a BMR below +10 per cent.

Probably the most reliable material for estimating the frequency of normal basal metabolic rates in thyrotoxicosis was provided by Means (1948). In a series of 1164 cases of thyrotoxicosis he found that about 12 per cent of the women and 8 per cent of the men had basal metabolic rates of +20 per cent or below.

Soisalo (1949) observed that 22 of 65 thyrotoxic patients had basal metabolic rates of +20 per cent or below. All these patients showed positive response to iodine. Hyperplastic thyroids were found in the fourteen patients in whom microscopical examination was carried out.

This evidence from the literature for the occurrence of normal basal metabolic rates in thyrotoxicosis is substantial. It is in agreement with the findings of the present investigation. There are some authors, however, who claim that thyrotoxicosis does not exist in the absence of an elevated BMR (M. Krogh, 1920; Boothby, 1921; Grafe, 1923; Kowitz, 1925; Merke, 1928; Morawitz, 1931; Simpson, 1948).

The second principal limitation which the BMR has in the diagnosis of thyrotoxicosis is its elevation or depression in diseases unrelated to the thyroid. It is often elevated in diseases of the blood and reticuloendothelial system, such as leukemia (Grafe, 1911; and others), polycythemia (Minot and Buckman, 1923), Hodgkin's disease and lymphosarcoma (Du Bois, 1936). It is not likely that these diseases would be confused with thyrotoxicosis, however.

Elevated basal metabolic rates may be observed in diseases of the endocrine glands, such as acromegaly (Boothby and Sandiford, 1922) and pheochromocytoma (Howard and Barker, 1937). Pheochromocytoma may even simulate thyrotoxicosis clinically (Rabin, 1929; and others).

It is important that elevated basal metabolic rates may occur in cardiovascular diseases because of occasional clinical confusion between such diseases and thyrotoxicosis. Peabody, Meyer, and Du Bois (1916), Hamburger and Lev (1925), and others observed increased BMR's in cardiac diseases with dyspnea. An elevated BMR has been observed in coarctation of the aorta (Blackford, 1928). Smith and Levine (1947) observed that certain patients with aortic stenosis manifested a persistent elevation of basal metabolism even when dyspnea and pulmonary congestion were minimal or absent. Furthermore, a few patients with aortic stenosis presented clinical features resembling those of thyrotoxicosis. These patients did not respond to iodine, however, and at operation their thyroid glands were completely normal even microscopically. In essential hypertension the BMR may be increased (Boothby and Sandiford, 1922; Rosenkrantz and Marshall, 1947). Furthermore, hypertension may simulate thyrotoxicosis clinically (Riesman, 1919; Boas and Shapiro, 1925).

Tremor may increase the metabolism (Magnus-Levy, 1906). It is well known that fever increases the metabolism.

On the other hand, there are certain nonthyroid diseases that decrease the BMR, such as anorexia nervosa (Eggert Møller, 1925) and Addison's disease (Koehler, 1928). Prolonged bed rest may also decrease the BMR (Du Bois, 1936).

For a more complete discussion of diseases that affect the BMR the reader is referred to Du Bois (1936).

In spite of the fact that thyrotoxicosis occurs with normal basal metabolic rates and that other diseases may raise the BMR, there is no doubt that the determination of the BMR is of definite value in the diagnosis of thyrotoxicosis. Recently, however, such an authority on thyroid diseases as Wahlberg (1946) questioned the value of BMR determinations for the diagnosis of thyrotoxicosis. He held that the clinical determination of the BMR as it is carried out in most hospitals is of

doubtful value. His experience has shown that the BMR as a guide for the diagnosis of mild and borderline cases of thyrotoxicosis is so seldom of real value and so often misleading that it can be omitted from clinical use if it is not carried out in a well-qualified laboratory.

In conclusion, it may be said that the determination of the basal metabolic rate is useful in the diagnosis of thyrotoxicosis, provided that it is elevated and other causes for such an elevation can be eliminated. A normal BMR does not exclude the possibility of thyrotoxicosis. Thus, there is a definite need for more specific and accurate methods for the evaluation of thyroid function in clinical medicine.

Serum Cholesterol

The effect of the thyroid hormone on the blood cholesterol concentration has been used for diagnostic purposes in thyroid diseases.

Many investigators (Epstein and Lande, 1922; Mason, Hunt, and Hurxthal, 1930; Hurxthal, 1933 a; McElroy, Schuman, and Ritchey, 1938; and others) have reported that in thyrotoxicosis serum cholesterol tends to be low. In myxedema it is usually elevated (Mason *et al.*, 1930; and others).

Man, Gildea, and Peters (1940) found that those patients who had the lowest cholesterol values while thyrotoxic proved to have low values even when they had returned to a euthyroid state. Similarly those with normally high cholesterol values maintained a relatively high level (within normal limits) even when they had thyrotoxicosis. Thus, the most important factor governing the cholesterol level in thyrotoxicosis seemed to be the cholesterol concentration of the individual when in a euthyroid state. They considered the diagnostic value of cholesterol determinations slight but felt that they supplied corroborative evidence and might be used when accurate basal metabolism tests could not be obtained. Hurxthal and Hunt (1935) and Means (1948) were of the opinion that cholesterol determinations had a definite place as an adjuvant to other diagnostic procedures. For the diagnosis of myxedema, Hurxthal (1934) considered cholesterol determinations more valuable than BMR's.

A number of investigators (Luden, 1918; Gardner and Gainsborough, 1928; Levy, 1931; Bonilla and Moya, 1931; Brøchner-Mortensen and Eggert Møller, 1940; and others) have found that the serum cholesterol is usually normal in thyrotoxicosis. Foldes and Murphy (1946 b) found no statistical difference in cholesterols between normal and thyrotoxic individuals despite the fact that all cases of thyrotoxicosis with BMR's below +30 per cent were excluded. Thus, there is no agreement about the consistency of the finding of low serum cholesterol in thyrotoxicosis. It is also well-known that low cholesterols may occur in a variety of nonthyroid diseases.

The serum cholesterol rises during treatment of thyrotoxicosis (Hurxthal, 1933 b) and falls during treatment of myxedema (Hurxthal, 1934). It may thus be of value in following the course of these diseases.

It can be concluded that a cholesterol below normal does not signify thyrotoxicosis, nor does a normal value exclude the diagnosis. An elevated cholesterol makes the diagnosis of thyrotoxicosis less likely.

Blood Iodine

The concentration of iodine in the blood has been used as an indicator of thyroid activity by various investigators since Veil and Sturm (1925) observed that the total blood iodine was elevated in thyrotoxicosis and decreased in myxedema. Veil and Sturm also separated the whole blood iodine into alcohol-insoluble and alcohol-soluble fractions. Holst, Lunde, Closs, and Pedersen (1928) found that the alcohol-insoluble or "protein-bound" blood iodine was increased in thyrotoxicosis. They also observed a fall of this blood iodine fraction following treatment with Lugol's solution. Holst (1928) expressed the opinion that this blood iodine fraction represented the circulating thyroid hormone.

Subsequently there appeared many studies on the value of blood iodine determinations for the diagnosis of disturbances in thyroid function. These studies may be divided into two main groups:

1. determination of total blood iodine of whole blood or serum,
2. determination of precipitable (protein-bound) iodine of whole blood or serum.

It can be said at once that the protein-bound iodine should be a more accurate index of the circulating thyroid hormone than is the total blood iodine.

The determination of the total whole blood iodine has not become of particular value as a diagnostic aid in thyrotoxicosis. Therefore, it was not considered necessary to review the whole literature on this subject. The reader instead is referred to monographs by Elmer (1938) and Salter (1940) and papers by Perkin and Lahey (1940) and Curtis and Fertman (1945). A brief discussion of a few representative studies will be sufficient to indicate what may be achieved with this method. The largest series of patients was studied by Perkin and Lahey (1940). They compared the total whole blood iodine values in 1078 consecutive patients with clinical hyperthyroidism with those of 745 patients with no evidence of hyperthyroidism. The overlap was very marked. Fifty-six per cent of the hyperthyroid patients gave values within $\pm$ 2 σ[1] of the mean for the controls (present writer's analysis).

Curtis and Fertman (1945) found in a series of 142 thyrotoxic patients that 45 per cent of the patients had total whole blood iodines within $\pm$ 2 σ of the mean of the normals. Similar results were obtained by Unonius (1946), Soisalo (1949), and others.

Furthermore, Curtis and Fertman (1947) observed elevated total whole blood iodine values in a variety of diseases other than thyrotoxicosis.

On the other hand, Riggs, Gildea, Man, and Peters (1941) reported more satis-

[1] Standard deviation.

factory results from determinations of total whole blood iodine. They used the new permanganate acid ashing method of Riggs and Man (1940). They did not observe any overlapping of the normals (26 persons) and the patients with thyrotoxicosis (31 cases). Seven patients with doubtful thyrotoxicosis were observed to have elevated blood iodine values. The results of Riggs *et al.* (1941) suggest that the considerable overlapping of total whole blood iodine values in euthyroid and hyperthyroid patients as observed by most investigators may be at least partially attributed to unreliable analytical methods and technical difficulties in the analyses.

Klassen, Bierbaum, and Curtis (1940) and Riggs, Lavietes, and Man (1942) demonstrated that the erythrocytes contained very little or no iodine, and it became apparent that the plasma or serum iodine would be more suitable for iodine analyses than whole blood.

However, analyses of total serum iodine have not been extensively studied, as it soon became apparent that the protein-bound serum iodine fraction represented a better index of circulating thyroid hormone. Winkler, Riggs, and Man (1945) found that the total serum iodine was decreased in myxedema, and Winkler, Riggs, Thompson, and Man (1946) found it elevated in thyrotoxicosis. Furthermore, they did not observe any significant difference between the concentration of total serum iodine in one group of thyrotoxic patients and the concentration of serum protein-bound iodine in another group.

It is the protein-bound fraction of the blood iodine that has proved most promising in the diagnosis of thyroid disease. Analyses of the protein-bound fraction have the advantage of excluding the hormonally inert inorganic iodine, the concentration of which may vary considerably. The analyses have been made either on whole blood or on plasma or serum. The results of the analyses of protein-bound whole blood iodine as reported by various investigators are summarized in Table 1. Most investigators have analyzed the alcohol-insoluble blood iodine fraction, but a few have studied the acetone-insoluble fraction. The methods for the iodine determinations have varied. Because of these methodological differences no great importance can be attached to the absolute magnitude of the values. From the clinical point of view it is the relation between the values observed in patients with disturbed thyroid function and those in normal controls that is important. The fact that various investigators, using exactly the same methods, obtain such different results is, however, disturbing and casts doubt upon the validity of determinations of protein-bound whole blood iodine.

In several investigations only a small number of patients were studied. The results in general indicate that the protein-bound whole blood iodine (alcohol-insoluble or acetone-insoluble) is above normal in thyrotoxicosis and below normal in myxedema.

For the diagnostic use of such iodine analyses it is necessary to know the degree of overlap among various groups. This estimation could not always be carried out because the number of patients was too small or the results not presented thoroughly

Table 1. **The protein-bound iodine of whole blood in various states of thyroid function.**

Author	Method	Protein-bound iodine of whole blood			
		Number of patients	Diagnosis	Average μg per cent	Observed range μg per cent
Veil and Sturm (1925)	v. Fellenberg	4	Normal	8.5	6—11
	Fractionation with alcohol	3	Hyperthyroidism	26	20—32
Lunde, Closs, and Pedersen (1929)	v. Fellenberg (modified)	—	Normal	—	1—4
	Fractionation with alcohol	3	Thyrotoxicosis	—	18—36
Nuernbergk and Widmann (1931)	Lunde, Closs, and Pedersen	—	Normal	12	—
		10	Thyrotoxicosis	95	—
		21	Vegetative neurosis simulating thyrotoxicosis	51	—
Dodds, Lawson, and Robertson (1932)	Lunde, Closs, and Pedersen	16	Normal	4.0	2.4— 5.8
		9	Hyperthyroidism	29.3	5—71
		29	Hyperthyroidism (some patients on iodine treatment)	19.9	4—80
		6	Nontoxic goiter	13.2	7—19
		1	Hypothyroidism	—	11
Biilmann (1938)	Leipert (modified)	9	Normal	5.2	4.2— 6.8
	Fractionation with alcohol	6	Thyrotoxicosis	20.3	9.4—35.5
		5	Myxedema	2.7	1.4— 3.9
Davison, Zollinger, and Curtis (1942)	Leipert (modified)	16	Normal	0.88	0.51— 1.34
	Fractionation with acetone	11	Hypothyroidism	0.49	0.23— 0.63
		4	Cardiovascular disease	0.50	0.42— 0.71
Swenson and Curtis (1948)	Davison, Zollinger, and Curtis	—	Normal	0.88	—
			Thyrotoxicosis:		
		90	diffuse goiter	2.45	—
		114	nodular goiter	2.05	—
		178	Nontoxic nodular goiter	1.02	—

enough. However, Swenson and Curtis (1948) found that 11 per cent of patients with toxic nodular goiter gave values within $\pm$ 1 σ of the normal mean. Davison, Zollinger, and Curtis (1942) observed that seven of 11 patients with myxedema were within the values observed in normals. Furthermore, Nuernbergk and Widmann (1931) found overlapping of the values for patients with thyrotoxicosis and vegetative neurosis simulating thyrotoxicosis. Dodds, Lawson, and Robertson (1932) found that the alcohol-insoluble whole blood iodine also was elevated in all of six cases of nontoxic goiter and in one patient with hypothyroidism.

Thus, the results of the determinations of the protein-bound whole blood iodine do not appear to be satisfactory for diagnostic purposes. This may be due to difficulties in the analytical technique. It is possible that the presence of the extra organic matter in the red cells may have interfered with the analyses.

As practically no iodine was present in the erythrocytes (Klassen *et al.*, 1940; Riggs *et al.*, 1942), it became logical to use plasma or serum rather than whole blood for attempts to estimate the circulating thyroid hormone. It is now also well established that the estimation of the protein-bound plasma or serum iodine is the best available index of circulating thyroid hormone. There is no difference between serum and plasma protein-bound iodine (Winkler, 1947). They can, therefore, be used interchangeably. The results obtained by various investigators are summarized in Table 2. The results in general demonstrate that the serum protein-bound iodine is elevated in thyrotoxicosis and decreased in myxedema.

Salter, Bassett, and Sappington (1941) analyzed the serum protein-bound iodine (PBI) in 100 cases with various thyroid disorders and correlated the findings with the clinical picture and the BMR. The limits for normals were more or less arbitrarily chosen to be 4—8 μg. per cent. It can be seen from Table 2 that they obtained a good separation between the various groups of patients with disturbances in thyroid function. All patients with myxedema had subnormal PBI's. Of the 38 cases of thyrotoxicosis there were three patients with serum protein-bound iodine values within the normal range. Fifteen patients with the ophthalmopathic type of Graves' disease all had normal PBI's despite the fact that BMR's varied between −20 per cent and +36 per cent. Patients with hypermetabolism without symptoms of hyperthyroidism and patients with hypometabolism without symptoms of hypothyroidism all had normal PBI's. In 29 per cent of the cases the BMR was not compatible with the clinical diagnosis. In this category the PBI usually gave values which confirmed the clinical diagnosis, and the BMR turned out to be misleading. Thus the PBI proved to be a more reliable measure of thyroid activity than was the BMR.

Winkler (1947) on the basis of determinations of serum protein-bound iodine in 235 normal individuals stated that the normal protein-bound iodine varied between 3 and 8 μg. per cent. A statistical analysis of his results shows that eight of 83 thyrotoxic patients (10 per cent) had values within $\pm 2\ \sigma$ of the normal mean.

Riggs (1947) evaluated the clinical usefulness of serum protein-bound iodine analyses for the diagnosis of thyroid disturbances on the basis of 400 consecutive analyses. He considered 3.5 to 7.0 μg. per cent as the normal range. Values ranging from 3.0—3.5 μg. per cent and from 7.0—8.0 μg. per cent were considered borderline, where the normal was not distinctly separable from the abnormal. Below 3.0 μg. per cent was typical of hypothyroidism and above 8.0 μg. per cent characteristic of hyperthyroidism. Eighty-five per cent of the analyses were definitely compatible with the clinical impression and four per cent probably were so. In many of these patients the initial classification was not clear, but subsequent studies, often initiated by the results of the serum protein-bound iodine analyses, established the diagnosis with reasonable certainty. In eight per cent the analyses did not agree with the clinical impression. In all instances except one the iodine value was too high. The main cause of these elevated values was previous administration of organic iodine-containing

Table 2. The serum protein-bound iodine in various states of thyroid function.

Author	Method	Serum protein-bound iodine			
		Number of patients	Diagnosis	Average μg per cent	Observed range μg per cent
Salter, Bassett, and Sappington (1941)	Riggs and Man (1940) or Fashena and Trevorrow* (1936) Fractionation with acetic acid and heat	10	Normal	5.2	4.6— 5.9
		38	Hyperthyroidism	12.7	4.9—24.7
		1	Hyperthyroidism with normal BMR	—	8.8
			Ophthalmic type of Graves' disease:		
		5	subnormal BMR	4.7	3.9— 5.6
		8	normal »	6.2	4.2— 7.3
		2	elevated »	—	5.5— 7.1
		20	Hypothyroidism	2.5	0.8— 3.9
		12	Hypermetabolism without hyperthyroidism	5.7	4.0— 7.7
		9	Hypometabolism without hypothyroidism	5.5	4.3— 6.1
		5	Euthyroid with suspected thyroid disease	5.7	4.8— 7.4
Man, Smirnow, Gildea, and Peters (1942)	Riggs and Man Fractionation with zinc sulphate and sodium hydroxide	5	Normal	6.1	5.7— 6.6
		6	Hyperthyroidism	12.3	9.8—20.2
Lowenstein, Bruger, and Hinton (1944)	Trevorrow and Fashena (1935) Fractionation with zinc sulphate and sodium hydroxide	21	Thyrotoxicosis	10.9	7.5—21.3
		4	Nontoxic goiter	—	5.0— 7.7
		3	Anxiety state	—	5.6— 7.3
		1	Paroxysmal tachycardia	—	7.0
		1	Pheochromocytoma	—	2.1
Winkler, Riggs, and Man (1945)	Riggs and Man Fractionation with zinc sulphate and sodium hydroxide	11	Hypothyroidism	1.2	0.2— 2.5
Winkler, Riggs, Thompson, and Man (1946)	Riggs and Man Fractionation with zinc sulphate and sodium hydroxide	—	Normal	—	3— 8
		37	Hyperthyroidism	13.9	—
Unonius (1946)	Leipert (modified) Fractionation with alcohol	16	Normal	3.2	0.5— 6.2
			Hyperthyroidism:		
		15	mild	5.5	1.4—12.3
		17	severe	10.0	3.2—23.8
		11	Nontoxic goiter	5.7	1.8—10.9
		7	Hypothyroidism	0.7	0.0— 3.2
Winkler (1947)	Riggs and Man Fractionation with zinc sulphate and sodium hydroxide	235	Normal	5.8	0.5—14.5
		83	Hyperthyroidism	13.5	5.5—36.5
		53	Nontoxic goiter	6.1	3.5—10.5
		26	Myxedema	1.3	0.5— 4.5
Riggs (1947)	Riggs and Man Fractionation with zinc sulphate and sodium hydroxide	55	Normal	5.1	3.5— 7.5
		50	Hyperthyroidism	12.8	8—23
		14	Myxedema	0.9	0— 2

* No distinct difference was observed between these two methods (Bassett, Coons, and Salter, 1941).

compounds used for roentgenographic visualization of the gall bladder, which may keep the PBI elevated for as long as a year. Organic iodine compounds used for pyelography more rarely cause trouble as they are rapidly excreted. Lipiodol, however, may keep the PBI elevated for years. In other instances the iodine values were elevated because the patients were receiving iodides without the laboratory being notified. In only three patients was the reason for the incompatible values not found. It was concluded that serum protein-bound iodine was an exceedingly valuable diagnostic aid.

On the other hand Unonius (1946) observed that ten of 15 cases of mild thyrotoxicosis had serum protein-bound iodines within $\pm 2\ \sigma$ of the normal mean.

In summary, the level of serum protein-bound iodine may be used as an index of the circulating thyroid hormone. It has been demonstrated by several investigators to be of great value for the diagnosis of disturbances of thyroid function. As a diagnostic aid it is far superior to the analysis of total iodine of whole blood and seems to be superior to the analysis of protein-bound iodine of whole blood. Unfortunately blood iodine analyses are complicated and time-consuming. They require the most careful analytical technique. Erroneous values may easily be obtained. It is likely that some of the discrepant results reported in the literature are due to faulty technique and inaccurate methods.

Iodine Tolerance Tests

The possibility for the development of an iodine tolerance test for clinical use depends on the physiological fact that the thyroid has a selective affinity for iodine. The experimental basis for this was established by perfusion experiments in dogs by Marine and Feiss (1915) and Marine and Rogoff (1916). They also found that hyperplastic glands with a low iodine content removed the greatest quantities of iodine from the perfusion fluid. Tissues other than the thyroid did not retain even traces of iodine.

The first actual use of this principle in studying iodine metabolism in thyrotoxicosis was made by Sturm (1927), who gave iodine by mouth and determined the urinary excretion after different intervals. He reported that most patients with thyrotoxicosis excreted less iodine than did normal subjects.

However, it was Elmer who first suggested in 1934 that such a test might be useful as a diagnostic aid in thyroid diseases. The test was based on his previous studies of iodine metabolism in normals (1932—33 a), in hypothyroidism (1932—33 b), and in hyperthyroidism (1933).

Since that time a number of iodine tolerance tests have been devised as a measure of thyroid activity. Some have been based on determination of the blood iodine, some on the urinary excretion, and some on the iodine retained in the thyroid. They will be discussed on this basis as follows:

I. The blood iodine curve following the administration of iodine.
   A. The rise in blood iodine.
   B. The disappearance of iodine from the blood.
II. The urinary excretion of iodine following the administration of iodine.
   A. With chemical methods.
   B. With radioactive iodine.
III. The collection of radioactive iodine by the thyroid.

I. The blood iodine curve following the administration of iodine

A. The rise in blood iodine

The rise in blood iodine following the oral ingestion of iodine as a diagnostic test for thyrotoxicosis was developed by PERKIN and his colleagues independently of ELMER (1934), though based on this previous work. The preliminary reports (PERKIN, BROWN, and LANG, 1934; PERKIN, LAHEY, and CATTELL, 1936) were followed by a definite statement of the results of the test in 108 patients (PERKIN and LAHEY, 1937). After normal individuals received 47 mg. of iodine (as Lugol's solution) the blood iodine values in 24 of 25 subjects reached a maximum of more than 100 μg. per cent. This peak value was obtained within the $2\,{}^{1}/_{2}$ hours during which observations were made. However, all patients with obvious thyrotoxicosis did not have maximal values below this critical level of 100 μg. per cent. Five cases of 25 showed a normal curve. Furthermore certain patients, both with nontoxic adenomatous goiter (2 of 25 cases) and with myxedema (4 of 5 cases), gave peak values in the thyrotoxic range. The test was felt to be of value as an adjunct in the diagnosis of borderline thyrotoxicosis. However, it is clear that the test is too insensitive for accurate diagnosis.

A similar test, but with intravenous administration of the iodine, was suggested by UNONIUS (1946). Only 15 cases with mild thyrotoxicosis were studied, and only nine cases fell below $\pm$ 3 σ of the normal mean. Too few cases were studied for definite conclusions.

B. The disappearance of iodine from the blood

On the basis of the studies of ELMER (1932—33 b, 1933) on the disappearance rate of ingested iodine from the blood, WATSON (1936) suggested an iodine tolerance test for the diagnosis of disturbances of thyroid function. Following the intravenous administration of 250 μg. of iodine (as Lugol's solution) per kg. body weight, he determined the relative amount of the iodine that remained in the blood six hours after its ingestion. In 1938 WATSON reported the results of the test in 80 patients. In 24 control (euthyroid) patients 5—38 per cent (average 18 per cent) of the injected iodine remained, while in 27 thyrotoxic patients the range of retention was

0—8 per cent. In 15 of the thyrotoxic patients the injected iodine had completely disappeared. In five thyrotoxic patients the values extended into the range of the controls. Following subtotal thyroidectomy the iodine left the blood much more slowly. Five patients with nontoxic goiter gave values within the range observed in the controls. In six cases of hypothyroidism 31—50 per cent was still in the blood after six hours, thus giving a certain amount of overlapping with the controls. It is of interest that in 18 patients with hypometabolism (BMR —15 to —38 per cent) but without clinical hypothyroidism there were five patients in whom the test gave results as observed in thyrotoxicosis. The degree of overlapping among patients with various states of thyroid function seems to be too large to make this test a very reliable diagnostic procedure.

Soisalo (1949) used an iodine tolerance test almost identical to that of Watson, but injected 200 μg. of iodine per kg. body weight instead of Watson's 250 μg. In 30 normal individuals the average retention after six hours was 17.1 ± 0.64 per cent, as compared to a retention of 4.3 ± 0.34 per cent in 68 thyrotoxic patients. An analysis of his results shows that three thyrotoxic patients were within ± 2 σ of the normal mean and 13 within ± 3 σ of the normal mean. Ten cases of nontoxic goiters gave normal values. Only five cases of nonthyroid diseases were studied, of which one gave a retention definitely below normal and two probably below normal. It should be mentioned that this test indicated thyrotoxicosis in a considerable number of patients with normal basal metabolic rates. Soisalo's results are very encouraging, though the degree of overlapping and the results in patients with nonthyroid diseases leave some doubt about the diagnostic value of the test. These results undoubtedly are better than those of Watson, which may be due to the smaller amount of iodine that was used. Thus, the results suggest that the amount of overlapping might be reduced by administering still smaller doses of iodine.

In conclusion, the iodine tolerance test based on the disappearance of iodine from the blood has not yet been developed into a reliable diagnostic test. The results reported by Soisalo indicate that the test can be improved. However, the practical value of the test is limited by the fact that iodine analyses are technically difficult and time-consuming. Both Watson and Soisalo considered the test too complicated for ordinary clinical use.

II. The urinary excretion of iodine following the administration of iodine

A. With chemical methods

For the diagnosis of thyroid disorders, particularly hypothyroidism, Elmer (1934) proposed determining the urinary excretion of iodine following its administration intravenously. The assumption was that the urinary excretion of iodine would reflect the thyroid's avidity for iodine. Similar tests have been used by other in-

Table 3. **The urinary excretion of iodine following a test dose.**

Author	Dose of iodine	Route of administration	Urinary excretion of iodine					Number of patients below euthyroid range
			Number of patients	Diagnosis	Average	Observed range	Period of urine collection hours	
Elmer (1934)	1300 µg	Intravenous	19	Euthyroid	16.6 %	11.7—20.5 %	6	
			10	Hyperthyroidism	17.1 %	0.8—29.0 %		2 of 10
			9	Nontoxic goiter	9.2 %	3.4—18.6 %		6 of 9
			17	Hypothyroidism	28.3 %	23.0—40.1 %		
Perkin, Brown, and Lang (1934)	50 000 µg	Oral	9	Normal	31.0 %	20.6—51.4 %	24	
			7	Hyperthyroidism	19.2 %	8.4—31.0 %		4 of 7
Watson (1938)	250 µg/kg body weight	Intravenous	23	Euthyroid	552 µg	44—1396 µg	6	
			26	Hyperthyroidism	403 µg	30—1734 µg		2 of 26
			5	Nontoxic goiter	706 µg	108—1580 µg		0 of 5
			5	Hypothyroidism	701 µg	15—1574 µg		
Unonius (1946)	130 µg/kg body weight	Intravenous	18	Euthyroid	49.0 %	34.3—68.0 %	24	
				Hyperthyroidism:				
			12	mild	29.5 %	10.0—60.5 %		8 of 12
			13	severe	22.3 %	8.0—35.3 %		12 of 13
			7	Nontoxic goiter	31.5 %	9.7—58.8 %		3 of 7
			3	Hypothyroidism	—	49.9—80.0 %		

The euthyroid subjects were collected among patients without known functional abnormality of the thyroid gland.

vestigators (Perkin, Brown, and Lang, 1934; Watson, 1938; and Unonius, 1946). The results as reported by various investigators are summarized in Table 3.

The table clearly indicates that there was a considerable overlapping among the various groups of patients. A comparatively large number of thyrotoxic patients gave values within the range observed in euthyroid individuals. Moreover, quite a few patients with nontoxic goiter excreted less than did the euthyroid subjects.

The results demonstrate that iodine tolerance tests based upon the quantitative chemical determination of iodine elimination in the urine do not have any definite value for the diagnosis of thyrotoxicosis. However, as will be seen from the following discussion, the urinary excretion of iodine under certain circumstances may reflect the functional state of the thyroid. The failure of this type of test in the diagnosis of thyrotoxicosis is probably due to the fact that such large amounts of iodine were used that differences in the thyroid's avidity for iodine could not be distinguished. However, physiologic doses of iodine would have been more difficult or impossible to use with this analytical technique.

B. With radioactive iodine

With the introduction of the radioactive isotope technique into the study of thyroid physiology by Hertz, Roberts, and Evans (1938) the possibilities for investigating

problems concerning thyroid diseases and iodine metabolism were enormously increased.

The basis for using radioactive isotopes as tracer substances in biology is that these isotopes remain chemically and physiologically identical with the naturally-occurring stable isotopes of the same element, provided that the radioactive isotopes are present in such small quantities that they do not produce any biologic effect by their radiation *per se*. Thus, radioactive iodine can be used to trace the course of a given quantity of iodine in biological processes.

In many studies of iodine metabolism it became possible to replace inaccurate and complicated chemical iodine analyses by more accurate and rather simple determinations of radioactive iodine. Due to the sensitivity of this technique it became possible to study the iodine metabolism with amounts of iodine within the physiological range. Furthermore, the isotope technique was especially suitable for the study of metabolic processes.

Hamilton and Soley (1939) were the first to employ radioactive iodine in the study of human thyroid disease when they determined the excretion of labelled iodine in the urine and feces in patients with various states of thyroid function. Subsequently a number of investigators made similar studies on the assumption that the urinary excretion of iodine reflects thyroid function. The general principle has been to administer a known amount of inactive (carrier) iodine labelled with radioactive iodine and then determine the percentage urinary excretion of radioactive iodine. Obviously the same percentages of radioactive and of inactive iodine are excreted. In fact, such experiments are simply iodine tolerance tests. The results of such tests as reported by various investigators are summarized in Table 4.

Hamilton and Soley (1939) observed similar excretion of radioactive iodine in euthyroid and hyperthyroid subjects (Table 4). The failure to demonstrate a lower excretion in thyrotoxic patients probably was due to the large amount of inactive (carrier) iodine, 14 mg., that was administered together with the radioactive iodine and also due to previous iodine treatment. When Hertz, Roberts, and Salter (1942) found an extremely wide variation in the excretion both among untreated and iodine-treated thyrotoxic patients, they considered this to be due to the great differences in the amounts of carrier iodine (0.1—325 mg.). Thus, when Hertz and Roberts (1942) limited the carrier to less than 2 mg. of iodine, they obtained results which suggested that the excretion of iodine might be less in hyperthyroid than in normal individuals. The number of patients was too small for any conclusions, however.

Subsequently there appeared a number of studies of the urinary excretion of radioactive iodine, in which the amount of carrier iodine varied from none to 300 μg. Whether this much variation in the carrier has affected the results cannot be stated from the literature. The considerable variation in the dosage of radioactive iodine (see Table 4) raises a similar problem which has not been studied.

Table 4. **The urinary excretion of radioactive iodine following a test dose.**

Author	Dose of inactive iodine micrograms	Dose of radioactive iodine microcuries	Urinary excretion of radioactive iodine					Remarks
			Number of patients	Diagnosis	Average per cent	Observed range per cent	Period of urine collection hours	
Hamilton and Soley (1939)	14 000	10—50	6	Euthyroid	79.7	70.3—87.2	48	
			1	Thyrotoxicosis	—	82.0		
			4	Thyrotoxicosis (previous iodine treatment)	79.8	70.3—87.3		
			3	Nontoxic goiter	—	49.9—78.1		
			2	Hypothyroidism	—	76.0—76.8		
Hertz, Roberts, and Salter (1942)	100—325 000	Not reported	8	Thyrotoxicosis	—	10—96	48—72	In some cases urine collection probably exceeded 72 hours
			4	Thyrotoxicosis (previous iodine treatment)	—	19—87		
Hertz and Roberts (1942)	< 2000	Not reported	1	Normal	—	62	72	
				Graves' disease:				
			6	classic	25	10—37		
			5	ophthalmopathic	46	32—56		
Rawson, Evans, Means, Peacock, Lerman, and Cortell (1944)	150	Not reported	11	Thyrotoxicosis on thiouracil	71	27—88	24	10 patients > 55 per cent
			1	Thyrotoxicosis	—	10		
Chapman and Evans (1946)	500	14 000—79 000	14	Thyrotoxicosis	34	9—86	48—72	11 patients < 50 per cent
Hertz and Roberts (1946)	< 2000	700—28 000	28	Thyrotoxicosis	32	6—85	72	21 patients < 50 per cent
Leiter, Seidlin, Marinelli, and Baumann (1946)	trace—300	600—5000	1	Thyrotoxicosis due to adenocarcinoma of the thyroid	—	30—40	72—96	
			1	Thyrotoxicosis possibly due to adenocarcinoma of the thyroid	—	12	96	
Keating, Power, Berkson, and Haines (1947)	100	100	4	Normal	65	60—70	48	The data for all groups obtained from excretion curves
			10	Euthyroid with thyroid carcinoma	65	50—75		
			16	Thyrotoxicosis	25	4—71*		* 14 patients
			6	Myxedema	78	70—84		< 50 per cent
Quimby and McCune (1947)	< 2	20—40	6	Euthyroid	70	62—79	48	All patients were children within
			1	Thyrotoxicosis	—	< 10		< 1—14 years of age
			1	Nontoxic goiter	—	71		
			1	Myxedema	—	70		
			3	Dwarfism	—	44—87		
			1	Pheochromocytoma	—	64		
Skanse (1948 a, 1948 b)	100	100	15	Euthyroid	66.6	52.7—84.1	48	Standard deviation: 8.6
			25	Thyrotoxicosis	19.2	6.2—32.3		» » 2.4
			6	Myxedema	—	72.4—91.7		
McArthur, Rawson, Fluharty, and Means (1948)	2—200	50—2000	30	Nonthyrotoxicosis	60	32—98	48	
			22	Thyrotoxicosis	25	7—45		
Werner, Quimby, and Schmidt (1948)	No carrier	40—100	30	Euthyroid	52	28—76	24	
			28	Thyrotoxicosis	17	6—27		
			4	Hyperophthalmic Graves' disease	22	18—25		
			5	Hypothyroidism	55	48—62		

All doses of iodine administered orally. The euthyroid subjects collected among patients with diseases not known to affect thyroid function.

Hamilton and Soley (1939) found that the urinary excretion of iodine in euthyroid and hyperthyroid patients was almost completed in 48 hours, while in hypothyroid patients the excretion proceeded over a longer period. With smaller doses of iodine similar observations have been made (Keating, Power, Berkson, and Haines, 1947; Werner, Quimby, and Schmidt, 1948).

In most of the studies the urinary excretion of radioactive iodine has been determined for a certain period of time, but Keating *et al.* (1947) also attempted to arrive at a more dynamic picture of the metabolism by a mathematical analysis of the urinary excretion curves. The data as reported by various investigators are rather incomplete for definite conclusions. There are no studies of the urinary excretion of radioactive iodine in healthy subjects except for scattered observations. Patients with a variety of diseases not known to affect thyroid function were usually used for the comparison with the patients with thyroid disturbances. In several investigations, the number of patients is too small to permit definite conclusions. Furthermore, a thorough analysis of the results is not always given.

The values for the excretion of radioactive iodine in euthyroid and thyrotoxic patients as reported by various investigators agree rather well (Table 4). The results demonstrate that the average excretion is less in thyrotoxic patients than it is in euthyroid individuals. However, the comparison cannot be made for all the studies included, as some were carried out for other purposes and do not include euthyroid subjects. There are two such studies dealing with excretion of radioactive iodine after thyrotoxic patients received therapeutic doses of radioactive iodine (Chapman and Evans, 1946; Hertz and Roberts, 1946). Another deals with the effect of thiouracil on thyroid function (Rawson, Evans, Means, Peacock, Lerman, and Cortell, 1944). The urinary excretion of radioactive iodine in two patients with thyrotoxicosis and carcinoma of the thyroid was reported by Leiter, Seidlin, Marinelli, and Baumann (1946).

The extent of overlapping between thyrotoxic and euthyroid patients varies considerably in the different studies and was not always analyzed statistically. Keating *et al.* (1947) found three of 16 patients with thyrotoxicosis within $\pm 2\ \sigma$ of the mean of the euthyroid patients. McArthur *et al.* observed that 6 of 22 thyrotoxic patients gave excretion values within the observed range of nonthyrotoxic patients (no statistical analysis). On the other hand Skanse (1948 b) observed no overlapping within $\pm 3\ \sigma$ of the mean of euthyroids, and Werner *et al.* (1948) found no thyrotoxic patient within the observed values of the euthyroids (no statistical analysis). The extent of overlapping probably depends upon the composition of the clinical material.

Urinary excretion of radioactive iodine in myxedema is reported in too few instances to permit any definite conclusions. The observations indicate that the total excretion often falls within the range observed in euthyroid individuals (Table 4). It seems to be fairly characteristic, however, that in myxedema the excretion is less abrupt, so that during the second day (24—48 hour period) the amount of

radioactive iodine excreted exceeds that excreted by euthyroid subjects (Hamilton and Soley, 1939; Keating *et al.*, 1947; Skanse, 1948 b).

The fecal excretion was studied by Hamilton and Soley (1939). It varied between 0.06 and 2.82 per cent with the exception of one case (11.25 per cent). This latter value was probably due to mixing of feces and urine.

A mathematical analysis of the urinary excretion curves by Keating *et al.* (1947) led to the calculation of the rate at which the radioactive iodine was collected by the tissues, disappeared from the blood, and was excreted in the urine. In so far as the thyroid represents the chief tissue for iodine collection, the collection rate was taken as an index of thyroid activity. They considered the collection rate to be less than normal in hypothyroid cases and much greater than normal in hyperthyroid patients. The disappearance rate was less in hypothyroid patients than in normal subjects and was greater than normal in hyperthyroidism. The renal excretion rate among the four groups of cases studied did not show any significant differences. The calculations were based on the results from a relatively small number of patients. It is likely, however, that this approach will prove profitable for the study of thyroid function in humans. From the clinical point of view, however, such tests must be considered too complicated.

A number of investigators have suggested that the urinary excretion of radioactive iodine might be useful in the diagnosis of thyrotoxicosis (Quimby and McCune, 1947; McArthur *et al.*, 1948; Skanse, 1948 a, 1948 b; Werner *et al.*, 1948). Their studies, however, do not adequately establish the reliability of the test. Skanse (1948 a) observed patients with thyrotoxicosis where the test undoubtedly was of diagnostic value, but the number of cases was small. McArthur *et al.* concluded that a finding of a low urinary excretion of radioactive iodine aided in the diagnosis of thyrotoxicosis in clinically equivocal cases and that a high urinary excretion was of assistance in excluding thyrotoxicosis in borderline cases where a true basal metabolic rate could not be obtained. It must be pointed out, however, that inasmuch as they observed a high extent of overlapping between the excretion values of thyrotoxic and nonthyrotoxic patients, the diagnostic value of the test appears to be limited. The considerable overlap may have been due to the heterogeneous group used as controls. From the data of Werner *et al.* (1948) it is difficult to estimate the diagnostic value of the test. They did not consider the urinary excretion as reliable a test as direct measurements of the uptake of radioactive iodine in the thyroid gland.

In children the diagnosis of thyrotoxicosis may present great difficulties as their basal metabolic rates are often unreliable. Quimby and McCune therefore suggested a radioactive iodine tolerance test as an aid. They doubted that the test would prove of value in children since complete urine collections are difficult to obtain, and they recommended the use of direct determinations of the collection of radioactive iodine by the thyroid.

The evaluation of the urinary excretion of radioactive iodine as a test in the

diagnosis of thyrotoxicosis has been hindered by the lack of data from normal subjects and from patients with diseases simulating thyrotoxicosis. The data from thyrotoxic patients are also rather meager.

In conclusion, the urinary excretion of radioactive iodine is smaller in patients with thyrotoxicosis than in euthyroid patients, provided that the amount of inactive carrier iodine administered with the radioactive iodine is kept small, of the magnitude of 100—200 μg. In view of this finding, it is not surprising that iodine tolerance tests based upon chemical methods did not adequately differentiate between normal subjects and thyrotoxic patients, as iodine was usually given in large doses.

Thus, there is some evidence that the urinary excretion of radioactive iodine may prove a valuable aid in the diagnosis of thyrotoxicosis. However, no adequate study of the diagnostic value of the procedure has been reported that clearly justifies the use of the test in the clinic.

III. The collection of radioactive iodine by the thyroid

The iodine tolerance tests thus far discussed have attempted to appraise thyroid function indirectly. With the introduction of radioactive iodine into the study of thyroid diseases, methods became available for direct *in vivo* determination of the collection of iodine by the thyroid. This approach was possible as the two commonly used isotopes of iodine, I^{130} and I^{131}, both emit gamma radiation which is penetrating enough to be detected outside of the body.

Hamilton and Soley introduced the *in vivo* measurement technique in 1939. Briefly the technique consists of orally administering a tracer dose of radioactive iodine and then recording the activity over the thyroid gland with a Geiger-Müller counter.

In studying thyroid function with this method there have been two general approaches:

1. repeated determinations of the radioactivity in the thyroid with construction of a collection curve.
2. a single quantitative determination of the radioactivity in the thyroid after a given period of time.

In a number of studies reported in the literature both approaches have been used together. In the present investigation the latter method was employed alone. However, it is necessary to review the results obtained with both approaches in order to interpret the present findings.

In the construction of a collection curve the activity may be directly expressed as the observed counting rate. This counting rate is an arbitrary unit and will depend on the amount of radioactive iodine administered and the type of instrument which is used for its detection. Obviously any other type of arbitrary unit may be used.

A number of investigators have tried to quantitate the curves and have expressed the results as a percentage of the administered dose. Regardless of the units used, the shape of the collection curve is unaffected.

The shape of the curve will be affected, however, by the amount of inactive (carrier) iodine that is administered with the radioactive tracer. For example, the collection curves observed in thyrotoxic patients by HAMILTON and SOLEY in 1940 when 14 mg. of carrier iodine were used differed from those observed when 0.1 μg. of carrier iodine was used (HAMILTON, SOLEY, REILLY, and EICHORN, 1943). These latter curves with the small amount of carrier were of an exponential shape, reaching a maximal value in about 24 hours in both euthyroid and hyperthyroid patients. The curves in thyrotoxic patients rose to a much higher level than did those of normal subjects. The maximal values in hypothyroid patients were lower than those of normal subjects except for two patients with hypothyroidism and large goiters whose curves resembled the thyrotoxic type. The number of patients was small as indicated in Table 5.

In similar studies HERTZ, ROBERTS, and SALTER (1942) observed that the composite collection curve for 12 patients with untreated thyrotoxicosis was higher than that of two normal individuals. HERTZ and ROBERTS (1942) also reported that the composite collection curve was higher in classic Graves' disease than in the ophthalmopathic type.

In 1947 ASTWOOD and STANLEY pointed out that the collection curve could be used to calculate the rate of accumulation of radioactive iodine. By plotting the radioactivity against the square root of time in minutes, a straight line was obtained. The slope of this line, the "accumulation gradient," provided a somewhat arbitrary numerical value for the collection rate. This method has the advantage that the results are independent of the size and location of the thyroid in the neck. The results obtained are indicated in Table 5. The overlapping between normal and mild thyrotoxic patients does not make it entirely suitable for diagnostic purposes (STANLEY and ASTWOOD, 1948).

Similar accumulation curves were obtained for euthyroid and thyrotoxic patients by LUELLEN, KEATING, WILLIAMS, BERKSON, POWER, and MCCONAHEY (1949), although the analyses were handled in a different fashion.

A different method for diagnostic purposes was suggested by STANLEY and ASTWOOD in 1948. After oral administration of an antithyroid drug to prevent the organic binding of iodine in the thyroid, a tracer dose of I^{131} was given. When the accumulation in the thyroid was maximal, a dose of potassium thiocyanate was given and the resulting discharge of radioactive iodine was followed. There were greater differences in the accumulation gradient between normal and thyrotoxic patients with this technique than without previous administration of an antithyroid drug. In addition, the discharge of radioactive iodine (induced by the thiocyanate) was more rapid in thyrotoxic patients than in normals. Although this test was considered useful for diagnostic purposes, no analysis of its reliability was presented.

Table 5. The uptake of radioactive iodine by the thyroid following a test dose.

Author	Dose of inactive iodine micrograms	Dose of radioactive iodine microcuries	Uptake of radioactive iodine by the thyroid					Remarks
			Number of patients	Diagnosis	Average	Observed range	Time after administration hours	
Hamilton and Soley (1940)	14 000	10—50	5	Normal	3 %	—	48	Values obtained from collection curves
			5	Thyrotoxicosis	3 %	—		
			2	Nontoxic goiter	12 %	—		
			4	Hypothyroidism	3 %	—		
Hertz, Roberts, and Salter (1942)	100—16 000	Not reported	2	Normal	1	—	48	Arbitrary units
			12	Thyrotoxicosis	7	—		Values obtained from collection curves
Hertz and Roberts (1942)	<2000	Not reported	2	Normal	11 %	—	48	Values obtained from collection curves
				Graves' disease:				
			6	classic	43 %	—		
			5	ophthalmopathic	22 %	—		
Hamilton, Soley, Reilly, and Eichorn (1943)	0.1	Not reported	3	Normal	20 %	—	48	Values obtained from collection curves
			3	Thyrotoxicosis	57 %	—		
			1	Nontoxic goiter	25 %	—		
				Hypothyroidism:				
			4	without goiter	2 %	—		
			2	with »	43 %	—		
Astwood and Stanley (1947)	No carrier	100	60	Normal	9.3	1.5—36.4		Accumulation gradients
			6	Thyrotoxicosis	25.8	17.0—43.6		
			3	Nontoxic goiter	—	1.5—19.0		
			4	Myxedema	—	<0.5—1.9		
Quimby and McCune (1947)	<2	20—40	33	Euthyroid	12 %	4—20 %	48	All patients were children within <1—14 years of age
			2	Thyrotoxicosis	—	34—60 %		
			1	Nontoxic goiter	—	3 %		
			1	Myxedema	—	<1 %		
			4	Cretinism	—	<1 %		
			7	Dwarfism	9 %	0.5—21 %		
			1	Pheochromocytoma	—	13 %		
Soley and Miller (1948)	No carrier	100—250	Not reported	Normal	—	<30 %	Not reported	
			Not reported	Thyrotoxicosis	—	40—80 %		
Werner, Quimby, and Schmidt (1948)	No carrier	40—100	30	Euthyroid	21 %	11—34 %	24	
				Toxic goiter:				
			28	diffuse	65 %	44—76 %		
			7	nodular	52 %	33—67 %		
			4	hyperophthalmic	58 %	54—60 %		
			3	Nontoxic nodular goiter	19 %	15—24 %		
			5	Hypothyroidism	3 %	1—4 %		

All doses of iodine administered orally. The euthyroid subjects collected among patients with diseases not known to affect thyroid function.

Keating, Wang, Luellen, Williams, Power, and McConahey (1949) suggested that the most exact method for measuring the collection rate was the determination of the thyroidal iodide clearance which was defined as the volume of plasma cleared of iodide per unit time. This clearance value was obtained from serial observations of the radioactive iodine in the plasma and from *in vivo* measurements over the thyroid simultaneously.

These various methods developed for the determination of the accumulation of radioactive iodine are complicated and time-consuming and at the present time hardly suited for practical clinical work.

For diagnostic purposes the methods based on the quantitative determination of the uptake of radioactive iodine in the thyroid have been more convenient. However, this quantitative determination is a difficult methodological problem due to the variations in size and location of the thyroid gland. There are two principal problems: the placement of the counter, and the choice of units. The counter has been placed directly on the neck (Hamilton and Soley, 1940; Hertz, Roberts, and Salter, 1942) or 15 cm. from the neck (Werner, Quimby, and Schmidt, 1948) or 29—53 cm. from the neck (Miller, Soley, and Dailey, 1948) or 53 cm. from the neck (Soley and Miller, 1948). It is obvious that differences in size and location of the thyroid will have a greater influence on the results when the counter is placed close to the neck. It might even be questioned whether good measurements can be obtained as near to the neck as 15 cm. The study of Evans and Evans (1948) indicates that this geometrical arrangement is not ideal. The distance used by Soley and Miller probably gives more reliable results.

The unit usually used to express the activity obtained over the thyroid has been a percentage of the administered dose. As a reference sample an aliquot or identical sample of the administered dose was in some instances simply placed as far from the counter as was the neck of the patient (Hamilton and Soley, 1939, 1940); in other cases it was put in a phantom-imitation of the human neck at a standard depth and in a standard sized receptacle (Soley and Miller, 1948; Miller, Soley, and Dailey, 1948); or with varying-sized receptacles (Quimby and McCune, 1947). It might be objected that it is hardly possible to arrange identical geometrical relations even with the phantoms. Undoubtedly there will be variations in such factors as absorption, scatter, geometry of the source, and even distance. Therefore, the use of a percentage unit cannot be considered accurate. However, the relative differences between patients with various thyroid disorders are of principal interest. Another procedure for obtaining percentage uptake was suggested by Hertz, Roberts, and Salter (1942). The percentage uptake in the thyroid at any given interval was calculated from the shape of the curve and from analyses of radioactive iodine in the excised thyroid.

The results as reported by various investigators are summarized in Table 5. The absolute values are not comparable for the reasons given above. The results in general have demonstrated that the amount of radioactive iodine collected by the

gland is proportional to the state of thyroid activity: thyrotoxic glands collect more iodine than do normals; myxedemic glands collect less. Nontoxic goiters usually behave as normal thyroids. When a large amount of carrier iodine was administered (Hamilton and Soley, 1940), the uptake 48 hours after the administration was about the same in euthyroid as in hyperthyroid patients. Obviously the large amount of carrier obscured the differences in the thyroid's avidity for iodine. Hertz and Roberts (1942) claimed that the thyroids accumulated less when associated with the ophthalmopathic type of Graves' disease than with the classic type. This was not substantiated by Werner, Quimby, and Schmidt (1948). In two patients with hypothyroidism and large goiters the uptake was as great as in thyrotoxic patients (Hamilton *et al.*, 1943).

It is difficult to draw definite conclusions from these studies. In most studies the number of cases was small. In several instances complete data were not published.

Various authors (Quimby and McCune, 1947; Astwood and Stanley, 1947; Werner, Quimby, and Schmidt, 1948; Soley and Miller, 1948) have suggested using *in vivo* measurements of the uptake of radioactive iodine as a diagnostic test for the differentiation of various diseases of the thyroid. For the diagnosis of thyrotoxicosis, however, there is the disadvantage that an appreciable overlap exists between euthyroid and thyrotoxic patients. In the largest series so far reported (Werner, Quimby, and Schmidt, 1949) it was observed that 40 of 97 thyrotoxic patients gave values within the limits observed in euthyroid subjects. Werner, Quimby, and Schmidt (1948) concluded that the direct measurement of the uptake of radioactive iodine was a more satisfactory test for thyroid function than was the determination of the urinary excretion. In children, where complete urine collections are difficult to obtain, the *in vivo* measurement method is preferable (Quimby and McCune, 1947).

It is probable that diagnostic tests based on the rate of accumulation of radioactive iodine in the thyroid will give a more accurate picture of the functional state of the thyroid than will the quantitative determinations of the total uptake. However, the former type of test is rather impractical for clinical work.

In conclusion, the *in vivo* measurement technique may offer a method for the clinical evaluation of thyroid function. However, the determination of the percentage uptake of radioactive iodine in the thyroid presents a difficult methodological problem, and the quantitative measurements used for this purpose have been rather inaccurate. Furthermore the relative merits of *in vivo* measurements of the uptake of radioactive iodine versus the urinary excretion of radioactive iodine as a diagnostic test have not been thoroughly studied.

Chapter III

METHODS

Physical and Chemical Properties of I^{131} as Used in the Present Investigation

$_{53}I^{131}$, which means iodine with an atomic number of 53 and a mass of 131, was used throughout for all diagnostic studies. In treatment I^{131} was chiefly employed, but in a few patients I^{130} was used.

I^{131} has a half-life of 8 days and is thus eminently suitable for biological experiments.

During the first part of this study the I^{131} was produced in the cyclotron at the Massachusetts Institute of Technology by bombardment of metallic tellurium with deuterons according to the following nuclear reaction:

$$_{52}Te^{130} + {}_{1}H^{2} \rightarrow {}_{53}I^{131} + {}_{0}n^{1}$$

During the chemical preparation of the cyclotron-produced isotope, carrier iodine[1] had to be added. Usually, however, the amount of inactive iodine per 100 microcuries (μc.) of I^{131} could be kept below 100 micrograms (μg.).

For most of the studies the I^{131} was obtained from the Oak Ridge National Laboratory, where it is produced in the chain-reacting pile by the bombardment of metallic tellurium with slow neutrons according to the following nuclear reactions:

$$_{52}Te^{130} + {}_{0}n^{1} \rightarrow {}_{52}Te^{131} + \gamma$$

$$_{52}Te^{131} \rightarrow {}_{53}I^{131} + \beta^{-}$$

The $_{52}Te^{131}$ has a half-life of 25 minutes, and thus rapidly decays into I^{131}. The I^{131} had an activity of 400—6100 μc. per ml. at the time of delivery.

The I^{131} from the pile was delivered as carrier-free iodide which meant that all the iodine atoms in the solution were radioactive, or at least should have been. The only inactive iodine present was that which occurred as a natural contaminant. Chemical analyses for iodine were made occasionally on one millicurie aliquots, and

[1] Iodine and iodide are used interchangeably, there being no case where molecular or nascent iodine enters into the discussion.

Table 6. **The maximal amount of contaminants in 100 μc. of I^{131}.**

Sulphate	0.1 mg.
Reducing agents (as oxalic acid)	0.08 mg.
Tellurium (radioactive)	0.09 μc.
Tellurium (inactive)	0.1 mg.

all gave negative results. With the method used this meant that there was less than 0.5 μg. of iodine present, probably much less.

Analyses for impurities were made at Oak Ridge before the isotope was shipped. From these data the maximal amount of impurities was calculated (Table 6).

No attempt was made to separate the I^{131} in a completely pure state as the concentration of the contaminants was too low to produce any biological effect or to influence the results of the experiments. Tellurium is relatively nontoxic. By far the majority of the "tracers" administered contained 0.01—0.04 mg. of tellurium. A dose of 0.1 mg. of tellurium can be considered absolutely harmless (Sollman, 1943).

The pH of the solution varied from acid to alkaline on arrival. The pH of acid solutions was brought to 8—9 with ammonium hydroxide, since iodine is much less volatile in an alkaline solution. On several occasions the half-life of the isotope was determined to be sure that the isotope received actually was pure I^{131}. The half-life was found to be 8.0—8.1 days, which is in good agreement with the results reported in the literature. (Livingood and Seaborg, 1938; Grummitt and Wilkinson, 1946).

A knowledge of the disintegration scheme of I^{131} is essential in order to standardize

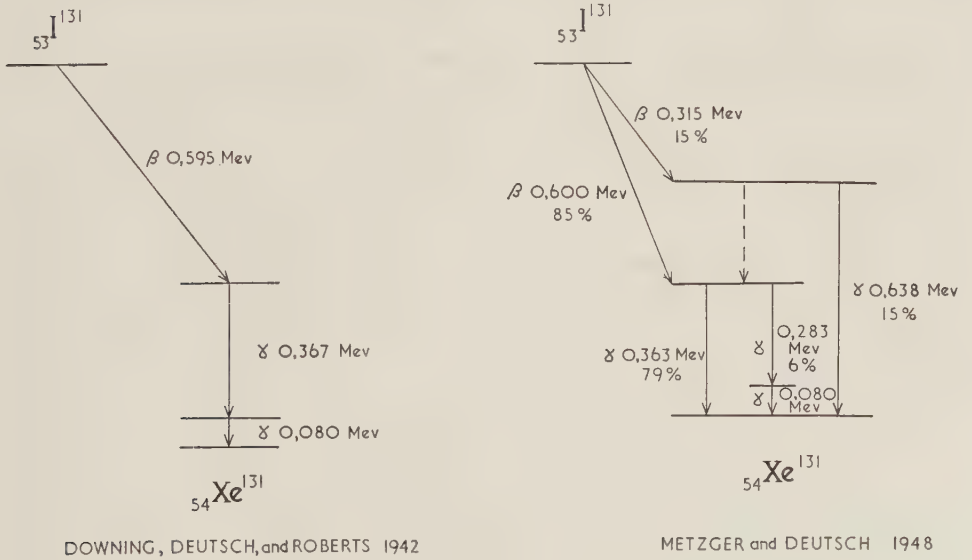

Fig. 2. The disintegration scheme of I^{131}.

the isotope in absolute units (curies). Downing, Deutsch, and Roberts (1942) established a simple disintegration scheme (Fig. 2). In standardizing the I^{131} with both beta ray and gamma ray measurements certain observations, incompatible with this scheme, were made by the present writer. The measurements based on beta rays gave too low values compared with those based on gamma rays. Absorption measurements by Davisson and Evans (1948) demonstrated the presence of a 0.650 Mev[1] gamma ray, the abundance of which was 15 per cent of the 0.367 Mev gamma ray. On the basis of these observations Metzger and Deutsch (1948) reinvestigated the radiations of I^{131} and proposed a new disintegration scheme (Fig. 2), which was much more complicated than that previously suggested. This new disintegration scheme roughly explains the inconsistencies which were observed by the comparative standardization of I^{131} from beta ray and gamma ray measurements.

Standardization of I^{131} in Absolute Units

One of the most fundamental problems in the use of radioactive isotopes is the complexity of their standardization in absolute units. A large part of ordinary tracer work in medicine and biology can be carried out without the need for absolute standards. Results may be expressed in terms of the administered dose, or in units compared to a standard source of known activity, or in some other arbitrary manner. However, in all experiments which involve radiation effects and therapeutic procedures, a standard absolute unit is essential. Comparison of the results of treatment is impossible unless the administered doses have been expressed in absolute units. In order to protect patients, animals, and workers, the absolute magnitude of both tracer and therapeutic doses must be apparent.

The temporarily employed absolute unit, the curie, is based upon disintegrations per unit time; standardization of any isotope in curies must therefore involve a similar measurement. As disintegration takes place in an isotope, radiation is emitted in all directions. A fraction of this enters the sensitive volume of the detecting instrument. Only a further fraction is registered by the detector.

The many problems of standardization are confusing to both the physicist and the biologist. The limitations of the equipment for detection and the incomplete understanding of the fundamental properties of radioactive isotopes have delayed clarification. The need for a satisfactory solution becomes more urgent as the use of radioactive isotopes steadily increases.

Unit of measurement

By definition a curie is the quantity of radon (0.66 $mm.^3$ at 0° C and 760 mm. mercury) in radioactive equilibrium with one gram of radium. A millicurie (mc.) is 0.001 curie and a microcurie (μc.) 0.000001 curie.

[1] Mev = million electron volt.

The absolute disintegration rate (the actual number of disintegrating atoms per unit of time) of radium has been determined by a number of methods. CURIE, DEBIERNE, EVE, GEIGER, HAHN, LIND, MEYER, RUTHERFORD, and SCHWEIDLER (1931) recommended that the value of 3.7×10^{10} disintegrating atoms per second per gram of radium should be used until the absolute value was known. This recommendation has been generally accepted.

When artificial radioactive isotopes were discovered and came into wide use, particularly in medicine and biology, the curie unit was extended to all sorts of radioactive isotopes despite the warning of CURIE *et al.* to restrict its use to the radium family. This led to a number of difficulties and caused considerable confusion. Thus, a millicurie of any isotope (for example, Na^{24}, P^{32}, I^{131}) meant the amount of the isotope which produced 3.7×10^7 disintegrating atoms per second. However, the determination of the absolute disintegration rate of any isotope is a difficult procedure.

Radium has been widely used as a standard to which other isotopes have been compared. It has, however, a complex gamma ray spectrum which is as different from that of other gamma ray emitters as these are different from each other. The instruments used to detect the radiation (for example, Geiger-Müller counters, electroscopes, and ionization chambers) have different efficiencies for gamma rays of various energies. Therefore, the fact that the same number of counts per unit time is recorded by a Geiger-Müller counter for both the "unknown" source and the "standard" radium does not mean that the atoms are disintegrating at the same rate in each sample. This simple fact is one important reason for the tremendous variation in isotope standardization among different laboratories.

The absolute disintegration rate of I^{131} as determined in the present investigation

In order to determine the absolute disintegration rate of a given isotope and thus correlate the curie unit with the number of counts measured by a Geiger-Müller counter, it is necessary to know:

1. the disintegration scheme of the isotope which is going to be measured, that is, the beta and gamma ray spectrum as well as the relative abundance and energy of all radiations that are emitted;
2. the absolute efficiency of the counter for various energies (as a function of energy of the particles), that is, the fraction of the emitted particles or quanta that are recorded by the instrument.

Fortunately the disintegration schemes have been determined for several isotopes of biological interest. For further information on this subject the reader is referred to the various published isotope charts; for example, that compiled by the Nuclear

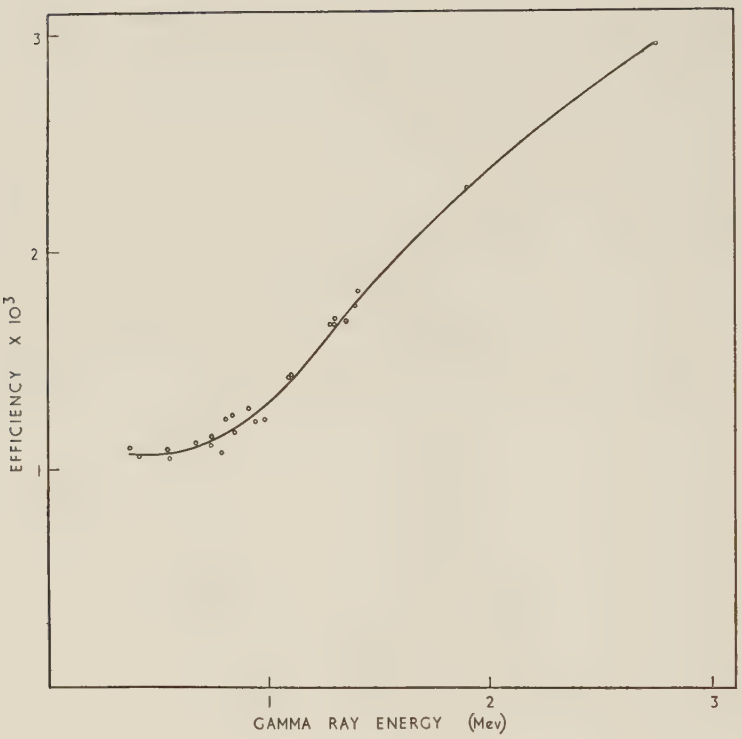

Fig. 3. The absolute efficiency of a standard gamma ray counter (platinum screen cathode) as a function of gamma ray energy according to Peacock (1944).

Data Committee of Clinton National Laboratory (Nucleonics, Vol. 2, No. 5, Part 2, May, 1948).

In order to determine the absolute efficiency of gamma ray counters PEACOCK (1944) used coincidence measurements of isotopes with known disintegration schemes. This procedure is feasible provided that the number and energy of the particles emitted per disintegration is known (DUNWORTH, 1940). Peacock used standard gamma ray counters, which can be made up with an efficiency within 1—2 per cent of the original counter. Measurements on a number of representative isotopes gave a curve of the efficiency of the standard gamma ray counter as a function of gamma ray energy (Fig. 3).

This calibrated counter can then be used to determine the absolute disintegration rate of the majority of gamma ray emitters provided that the disintegration scheme of the isotope is known and that the absolute disintegration rate is known for another gamma ray emitting isotope which is used as a standard. Isotopes with long half-lives are most convenient to use as standards.

Since the curie unit has been widely employed in the medical applications of radio-

active isotopes, it was considered natural to use it in this investigation despite the objections raised to its use outside the radium family.

In order to express the I^{131} in terms of curie units the activity of the I^{131} samples was compared with that of standard radium. Evans (1943) has reported measurements of the gamma ray energies and relative abundances of the gamma rays of radium in equilibrium with its decay products, and Peacock (1944) has determined the standard counting tube efficiency for the various gamma rays of radium. By adding their respective contributions to the counting rate of the standard counter the total efficiency for radium is obtained which for an unshielded standard counter of the type used by Peacock amounts to 2.92×10^{-3}. By coincidence measurements Peacock found an efficiency of 1.10×10^{-3} for I^{131}. The ratio

$$\frac{2.92 \times 10^{-3}}{1.10 \times 10^{-3}} = 2.65$$

therefore tells how much more efficient the standard counter is in detecting gamma rays from radium than those from I^{131}.

To obtain the absolute disintegration rate of a sample of I^{131}, the counting rates of the sample of I^{131} and of a known amount of radium must be determined under standardized conditions.

Then: Activity of I^{131} (μc.) =

$$\mu\text{g. of } Ra^{++} \times \frac{CPM_{I^{131}}}{CPM_{Ra^{++}}} \times 2.65 \qquad \text{(Eq. 1)}$$

CPM = net counts per minute.

In the present measurements, however, the standard counter was shielded with one-quarter inch (0.64 cm.) of aluminum to exclude beta rays. Therefore a correction had to be made for the absorption of the gamma rays in the aluminum. The transmission of the gamma rays from I^{131} and of those from radium in one-quarter inch of aluminum was determined experimentally:

$$\frac{I^{131} \text{ with } {}^1/_4'' \text{ Al around counter}}{I^{131} \text{ with counter unshielded}} = 96.5 \text{ per cent.}$$

$$\frac{Ra^{++} \text{ with } {}^1/_4'' \text{ Al around counter}}{Ra^{++} \text{ with counter unshielded}} = 91.5 \text{ per cent.}$$

Taking this absorption into account, the formula given above must be corrected as follows:

Table 7. **Intercomparison of standardization of I^{131}.**

Institution	Method	Value (millirutherford/ml[1])
Oak Ridge National Laboratory	Gamma ray ionization chamber calibrated by coincidence measurements	145
National Bureau of Standards	Coincidence measurements	147
Massachusetts Institute of Technology (the author's observations)	Gamma ray Geiger-Müller counter calibrated by coincidence measurements	145

[1] 1 millirutherford (mrd) $= 10^3$ disintegrations/sec.

$$\text{Activity of } I^{131} \ (\mu c.) =$$

$$= \mu g.\ \text{of}\ Ra^{++} \times \frac{CPM_{I^{131}} \times \frac{100}{96.5}}{CPM_{Ra^{++}} \times \frac{100}{91.5}} \times 2.65 =$$

$$= \mu g.\ \text{of}\ Ra^{++} \times \frac{CPM_{I^{131}}}{CPM_{Ra^{++}}} \times 2.52 \qquad \text{(Eq. 2)}$$

There is good evidence for assuming that this method of determining the absolute disintegration rate of samples of I^{131} is fairly correct. In an intercomparison undertaken by the National Bureau of Standards, Washington, D. C., the present measurements were in good agreement with those assumed to be correct (Table 7).

When the present investigation was completed, Metzger and Deutsch (1948) proposed a new disintegration scheme of I^{131} as discussed previously (pp. 27—28, Fig. 2). They found a 0.638 Mev gamma ray transition following 15 per cent of the beta rays of I^{131}. As this gamma ray was not known at the time of Peacock's studies (1944), his counting tube efficiency value for I^{131} is not absolutely correct. However, the deviation is so small that it can be disregarded. As can be seen from the curve (Fig. 3), the efficiency of the platinum screen gamma ray tube is almost independent of energy in the region between 0.4 and 0.7 Mev. Therefore a gamma ray of 0.638 Mev with an abundance of 15 per cent will change the total counting tube efficiency for I^{131} very little. It is estimated that the correction is less than five per cent.

Procedure for standardization of I^{131}

A platinum screen cathode Geiger-Müller counter was used. The cathode was constructed with 52 wires to the inch in either direction. The diameter of the counter was 2.5 cm. and the length of the cathode 11 cm. The anode was a 0.15 mm. tungsten

wire, silver soldered at each end to a segment of 1 mm. tungsten wire. These wires were in turn sealed into a glass counter envelope. The counter was filled with a mixture of argon and alcohol to a pressure of 100 mm. mercury. A characteristic curve of counting rate versus voltage for the counter was obtained to determine the operating potential. This curve was checked repeatedly to control the stability of the counter. The counter was operated 100 volts above the threshold. The resolving time was measured to be 4×10^{-6} minutes. The observed counting rates were corrected for the resolving time of the counter by means of the formula:

$$N = n(1 + n\tau), \text{ where}$$

τ = resolving time.
n = observed counting rate.
N = true counting rate.

The theoretical basis for this formula has been thoroughly discussed by Evans (1948).

This counting tube is an exact copy of the one that Peacock (1944) used for his determination of the efficiency of gamma ray tubes for gamma rays of different energies.

All measurements were made on a standard measuring set-up. A scaling circuit (scale of 64) with a mechanical recorder and an electric timer was used to record the counting rates. Usually the measurements were made at distances of 40—100 cm. depending upon the strength of the I^{131} source. Measurements demonstrated that for the arrangements used the inverse-square law was valid. However, for short distances the inverse-square law breaks down (Evans and Evans, 1948). It is also possible that the inverse-square law is invalid at long distances, probably because of scattering.

The procedure to determine the absolute disintegration rate for I^{131} then is to compare the counting rate for the I^{131} source with that of a standard radium source. The two sources are placed successively in the same position relative to the counter. Knowing the counting rate of the I^{131} source and that of the standard radium, the amount of I^{131}, expressed in microcuries, is obtained from Eq. (2).

The Effect of the Size of the Dose of I^{131} on its Excretion

Although the test for measuring thyroid function presented in this paper is standardized for a dose of 100 μc. of I^{131}, in certain situations other doses were used. The group of normal subjects was given 10 μc. each as a safety procedure to avoid every possibility of radiation damage to the thyroid. Certain patients with nontoxic goiters were given 500 μc. and others with malignant tumors of the thyroid received 1000—2000 μc. in order to obtain radioautographs of the resected thyroids. It was, therefore, necessary to establish that the size of the dose of I^{131} did not influence the urinary excretion.

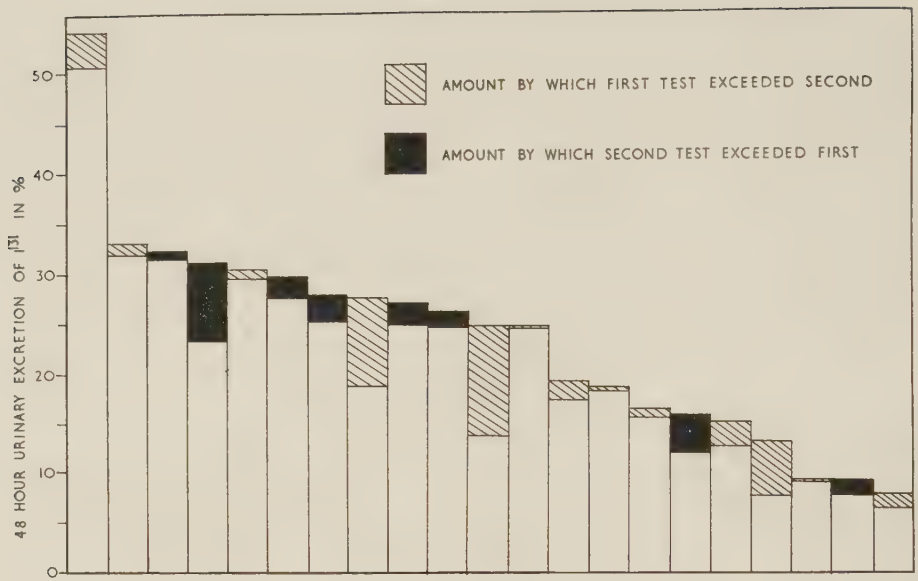

Fig. 4. The effect of varying the dose of I^{131}. Comparison of the urinary excretion of a tracer dose of I^{131} (first test) with that of a therapeutic dose (second test) some days later. Carrier iodine constant.

Evidence on this point was obtained from 21 thyrotoxic patients by comparing the excretion of a tracer dose (100 μc.) on one occasion followed by a therapeutic dose (6000—14000 μc.) two to six days later. Fig. 4 indicates the results of the two sets of tests. There was practically no difference between the two tests. The mean of the differences between the 48-hour urinary excretion of the tracer dose and the therapeutic dose of I^{131} was found to be $+0.72$ per cent of the administered dose with an $\varepsilon(M)$ of ± 0.90 per cent. The corresponding figures for the 0—24 hour period were $+1.34 \pm 0.87$ per cent. Thus the radiation from therapeutic doses of I^{131} does not affect the urinary excretion of I^{131} during the 48 hours following its administration.

From these observations it may be generalized that the variations of dosage used in these investigations had no influence on the urinary excretion. The lower limit for the dose of I^{131} will be set by the sensitivity of the methods used to measure the radioactivity in the urine.

The Effect of the Amount of Carrier Iodide on the Excretion of I^{131}

The amount of iodine in a tracer dose of I^{131} is exceedingly small. It is so small that an appreciable amount of it may be lost in the few simple maneuvers involved

in preparing for its administration. In order to increase the total amount of iodine given without increasing the radioactive material, a proportionally large amount of inactive iodide is added. This "carrier" iodide avoids the above difficulty. Of course, the quantity must not be so large that it will conceal differences in the avidity of the thyroid for I^{131}.

That a loss of I^{131} does take place in the absence of carrier iodide is indicated by the fact that simply pouring a weakly acid solution containing a few millicuries of carrier-free I^{131} from one glass container to another may result in appreciable losses, apparently by adherence to the glass. Such losses are understandable when one considers that the total amount of iodine in solution is so small. For example, in 1 mc. of I^{131} there are only 8.1×10^{-9} grams of iodine. If one assumes a constant loss of iodine by adherence to the glass, then the addition of a relatively large amount of carrier iodide (such as 100 μg. which is about 10,000 times more iodine than that in 1 mc. of I^{131}) will prevent the loss of I^{131}.

On the basis of this observation the decision was made to use carrier iodide throughout. It is possible that this precaution was unnecessary. Astwood and Stanley (1947), Werner, Quimby, and Schmidt (1948), and others have used carrier-free I^{131}, apparently without observing any disadvantages. The present writer considered it safer to use carrier.

The limits within which the amount of carrier iodide should fall may be judged from physiological considerations. It is estimated that about 50—100 μg. of iodine are required daily for the synthesis of a normal amount of thyroid hormone (Salter, 1940). In thyrotoxicosis the increased need for iodine is probably proportionally less than the increased output of thyroid hormone, as iodine from degraded hormone is reutilized by the thyroid. Thus, even in severe thyrotoxicosis the thyroid probably will not utilize more than a few hundred micrograms of iodine daily.

It is then understandable that changes in the thyroid's avidity for iodine were difficult or impossible to detect by chemical iodine tolerance tests where doses of several milligrams of iodine were used.

When Hamilton and Soley (1939) introduced radioactive iodine as a means of studying the iodine metabolism in humans they gave as much as 14 mg. of carrier iodide. Their failure to observe any differences in the urinary excretion of radioactive iodine between thyrotoxic and euthyroid patients is clearly illustrated by an example. Assume that the thyroid in one patient collected 100 μg. of iodine and in another 500 μg. of iodine. In the first patient the collection of radioactive iodine would be $\frac{100}{14000} = 0.71$ per cent and in the second, $\frac{500}{14000} = 3.55$ per cent if the small amount of iodide already present in the blood serum is neglected. Despite a five times increased uptake of iodine by the thyroid, the urinary excretion would not differ by more than 3—4 per cent. Such a difference might not be demonstrated even with radioactive iodine.

Hertz, Roberts, Means, and Evans (1940) observed in rabbits that the per-

centage uptake of radioactive iodine by the thyroid varied inversely with the dose of carrier iodide.

These studies indicated that a small dose of carrier iodide would be preferable for a radioactive iodine tolerance test. Theoretically, carrier-free I^{131} would be desirable as the I^{131} under such circumstances would really picture the iodine metabolism. Certainly the quantity of iodine in a tracer dose of I^{131} can be disregarded from the physiological and chemical point of view. For example, in a 100 μc. dose of I^{131} there are 8.1×10^{-10} grams or approximately 0.001 μg. of iodine.

There were several reasons for avoiding the use of such minute amounts of iodine. The previously discussed losses of I^{131} from carrier-free solutions gave a definite warning. Postprandial variations in the normal blood iodide concentration would probably give undesirable variations in the excretion of I^{131}. Radioactive iodine produced in a cyclotron could not easily be prepared free of carrier. Therefore, the problem was to choose a quantity of carrier that was adequate but not excessive.

Evidence concerning a satisfactory amount of carrier iodide is found in studies on 15 patients who were given repeat tests with 100 μg. of carrier iodide on the first occasion and 10 μg. on the second. Complete urine collections were obtained in all patients for 24 hours, while the collection for 48 hours was complete in only 10 patients. For the purpose of these experiments a 24-hour period may be considered adequate, as a comparatively small amount of I^{131} was excreted during the second 24-hour period.

Figure 5 presents the results of the 24-hour excretion of I^{131}. There was no significant difference between the two tests. The mean of the differences of the 24-hour excretion of I^{131} between 100 μg. and 10 μg. of carrier iodide was $+0.09$ per cent of the administered dose with an ε (M) of ± 0.93 per cent. The corresponding figures for the 48-hour excretion were $+0.96 \pm 1.65$ per cent.

From these observations it can be concluded that the carrier iodide has no influence on the urinary excretion of I^{131} when 100 μg. or less is used. Thus, the carrier had no effect in a few tests in which the I^{131} was obtained from the cyclotron and the inactive iodide varied between 4 μg. and 100 μg. There were also a number of patients with nontoxic goiter, who were used for certain other studies as well, and who received 10 μg. of carrier. The present studies do not permit any definite conclusions as to the upper limit for the amount of carrier that can be used without affecting the urinary excretion of I^{131}. Observations in a few patients demonstrated that the limit is below 1000 μg. of iodide. The limit probably is closer to 100 μg., as was indicated in Case 15 where the 48-hour excretion of I^{131} was 22.7 per cent with 4 μg. of carrier and 39.6 per cent with 370 μg. When therapeutic doses of ordinary iodide (I^{127}) are administered, the excretion of I^{131} increases considerably (see p. 87).

The use of 100 μg. of carrier probably does not influence the avidity of the thyroid for I^{131}. There are two aspects to be considered. Firstly, this quantity of iodine is not likely to effect any involutionary changes in the gland. The normal plasma iodide has a concentration of about 2 μg. per cent, and this iodine fraction is relatively

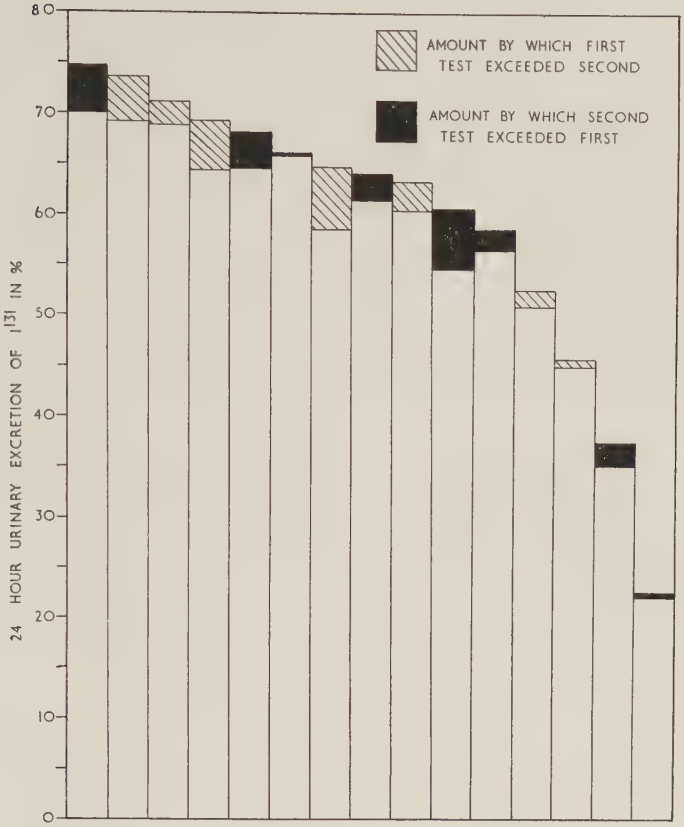

Fig. 5. The effect of varying the carrier iodine. Comparison of the urinary excretion of a tracer dose of I^{131} with 100 μg. of carrier iodine (first test) and with 10 μg. of carrier iodine (second test). Tracer dose constant.

constant even in thyrotoxicosis (Bassett, Coons, and Salter, 1941). The carrier of 100 μg. would temporarily increase the blood iodide concentration by about 0.5—1 μg. per cent. Such a small increment of blood iodide concentration probably would have no pharmacologic action on the thyroid. Secondly, the carrier iodide is too small to increase appreciably the total amount of available iodine and thus conceal differences in the thyroid's avidity for iodine.

It should be remembered that in the radioactive iodine tolerance test the I^{131} measures not only the excretion (or the collection by the thyroid) of the carrier iodide but also of all the iodide in the body that is in equilibrium with the I^{131}. This is certainly true for the normally occurring blood iodide and may be true for the iodide in the extracellular fluid.

In conclusion, the urinary excretion of I^{131} is not influenced by carrier in amounts of 100 μg. or less. The upper limit for the amount of carrier that does not affect

the excretion of I^{131} is less than 1000 μg. Unexpected losses of I^{131} may occur if no carrier is used. In the present studies 100 μg. of carrier iodide has been found to be a suitable amount.

Procedure for the Radioactive Iodine Tolerance Test[1]

1. The tracer dose of I^{131} (usually 100 microcuries) with 100 micrograms of inert iodine (sodium iodide) as a carrier is made up to 100 ml. One ml. is taken off as a standard.
2. The tracer dose is given orally, preferably in the morning before breakfast.
3. The urine is collected for 48 hours in two 24-hour specimens following the administration of the I^{131}.

As long as the urinary excretion is expressed in per cent of the administered dose, the size of the dose of I^{131}, at least within wide limits, does not influence the urinary excretion of I^{131} (see p. 34). However, it is necessary to know the size of the dose of I^{131} in absolute units to avoid radiation hazards.

The tracer dose should be given in such a way as to prevent losses of radioactivity in the container, the mouth, and the esophagus. It is entirely sufficient to rinse the container twice and have the patient drink the wash-water.

The presence of food in the stomach may delay the absorption of iodine. It might therefore be an advantage to give the I^{131} while the patient is fasting. However, the administration of the I^{131} following a meal has no effect on the urinary excretion of I^{131} over a period as long as 24 hours. The fact that the patient does or does not void immediately before the I^{131} is administered does not influence the test.

In order to study certain problems concerning the dynamics of iodine metabolism, the urine in one series of patients was collected in four specimens: 0—6 hours, 6—12 hours, 12—24 hours, and 24—48 hours.

Instructions concerning the collection of urine were carefully given to the patient. If there was any doubt regarding the completeness of the urine collection, the test was discarded. The urine was collected in glass bottles and the urinary volumes were carefully measured.

Apparatus for Measuring Radioactive Samples

Geiger-Müller counter

Mica window, bell type beta ray counters were used throughout for the measurements. This type affords thin windows and large solid angles. The design has been described by Good, Kip, and Brown (1946). (See Fig. 6.) The cathode consists

[1] The method for the direct measurement of the uptake of I^{131} by the thyroid is presented in Chapter X.

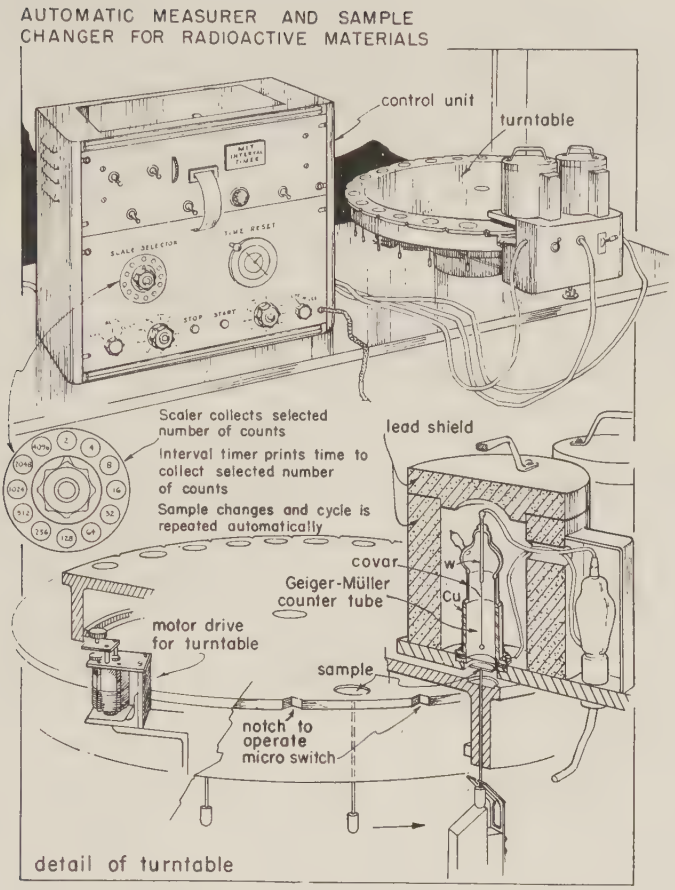

Fig. 6. The automatic measuring device.

of a copper tubing which is silver-soldered on the top to a ring of Covar[1] and on the bottom to a flange of steel. The anode is made of tungsten and has a glass bead at its free end to prevent corona discharge. The mica window is made to a thickness of 3—3.5 mg./cm^2 (approximately 10 microns). The periphery of the mica window is sandwiched between two 0.15 mm. lead gaskets, and, to insure that the tube is air-tight, the periphery is painted with a very light coating of Glyptol.[2] The gas filling is a mixture of helium (or argon) and alcohol in the proportion of 9:1 at a pressure of 100 mm. mercury.

Automatic measuring device

In order to carry out the large number of analyses of radioactive iodine necessary in this study, an automatic counting and recording apparatus was used for many

[1] Covar: alloy of iron, nickel, cobalt, and manganese.
[2] Glyptol: a synthetic lacquer.

of the measurements. This apparatus was devised by Peacock and Good (1946), and the reader is referred to their paper for the details of the construction. The apparatus consists of an automatic turntable, a scaling circuit, and an interval timer. Fig. 6 gives a schematic picture of the arrangement. The turntable has 24 sample holders around the perimeter. For each 15-degree shift of the turntable a new sample is placed under the Geiger-Müller counter. The rotation of the turntable is controlled by the scaler. In the arrangement seen on Fig. 6 an Autoscaler manufactured by Tracerlab, Boston, was used. This scaler is adjustable to count from 2 to 4096 counts. However, any sort of scaling circuit can be used. The scaler is connected to an interval timer which stamps the elapsed time to the nearest 100th of a minute on a paper tape after the desired number of counts have been collected.

Preparation and Measurement of Urine Samples

In measuring samples containing radioactive iodine, silver-plated copper planchets, 0.25 mm. thick and 2.5 cm. in diameter, are used. Silver nitrate (0.20 ml. of a solution containing 1 mg. Ag. per ml.) mixed with a small amount of a wetting agent (Duponol)[1] is placed on the planchets. The Duponol lowers the surface tension and thus a more uniform spreading of the radioactive iodine sample is achieved. A 0.2 ml. aliquot of each urine sample is pipetted with sugar pipettes and mixed with the silver nitrate-Duponol on the planchet. A precipitate of silver iodide is formed. For convenience in counting, the original 1 ml. aliquot of the tracer dose is diluted with 5 ml. of NaI (total 50 μg. of iodine). A 0.2 ml. aliquot of this solution is used for measurement exactly as the urine specimen. The urine specimen and standard are prepared in duplicate.

The samples are rapidly and conveniently evaporated to dryness with heating lamps. The samples should be completely dry before measurement to avoid absorption of beta radiation by moisture. The dry samples are then placed on the sample holders of the automatic turntable.

Depending upon the scaling circuit used, either 4096 or 6400 counts are taken twice for each planchet or four times for each urine sample and each standard. Therefore at least 16,000 counts are taken on each sample or standard which affords sufficient accuracy. The error in counting will be less than one per cent.

From the data obtained by this method the number of counts for the whole urine specimen and for the total administered dose is calculated (Table 8). Then the percentage of radioactive iodine excreted is easily found, as demonstrated in the table. No correction for radioactive decay is necessary since the standard was prepared from the original dose and is therefore decaying at the same rate as the portion of the dose in the urine.

[1] Obtained from Du Pont Chem. Co.

Table 8. Sample data sheet.

Sample	Read* (min)	Read (min)	Average	Total CPM**	Net CPM	Dilution	Total volume	Total activity (CPM)	Excretion (per cent)
Background	269.68	273.00	271.34	26†					
Case 79									
Urine $^{3}/_{16}$—$^{3}/_{17}$	4.36	4.48	4.46	1435	1409	$\times \frac{1}{0.2}$	$\times$ 650	$=4.58 \times 10^{6}$	24.2
	4.35	4.63							
» $^{3}/_{17}$—$^{3}/_{18}$	124.02	125.00	124.60	51	25	$\times \frac{1}{0.2}$	$\times$ 1490	$=1.86 \times 10^{5}$	0.98
	124.45	124.92							
Standard	1.02	1.00	1.00	6400	6374	$\times \frac{6}{0.2}$	$\times$ 99	$=1.89 \times 10^{7}$	—
	0.98	1.00							

* 6400 counts for each reading.

** CPM=counts per minute.

† Counting rate without sample, primarily due to cosmic radiation.

Practical Considerations in the Use of this Technique

In operating such an automatic turntable there are several important factors that must not be overlooked. It is absolutely necessary that the samples always be at the same distance from the counter window. Therefore, the length of the sample holders has to be checked repeatedly. This can be done with an accuracy of 0.1 mm. In order to simplify placing the samples in the same horizontal position with respect to the counter window, the planchets and sample holders are made of exactly the same size. Calibration of the scaling circuit is done by the use of a standard 60 cycle alternating current.

On one of the sample holders of the turntable there is placed a Radium D+E standard (half-life 22 years). This standard serves as a check on the beta ray counters so that one will know whether they are operating identically day after day and be warned if they are not.

The characteristic curve of the Geiger-Müller counter should be carefully checked repeatedly. Also a rough checking every day is recommended. If the threshold value changes or if the plateau starts to shrink, it usually indicates that the counting tube is breaking down, and the results thus become unreliable.

Increase in background counting rate is usually an indication of breakdown of the Geiger-Müller tube. It is a good rule to take background readings both before and after the measurements of the radioactive samples to insure accuracy.

Though it seems obvious, it might be pointed out that the counting tube always should be carefully grounded, to avoid the possibility of spurious counts.

If the measurements are not reproducible, it usually saves time to check the high voltage before further search for the error is made. The mechanical register should also be checked. It sometimes happens that the voltage of the impulses is too low to be registered.

In preparing the samples one must pay attention to several practical details. The planchets should be absolutely flat, or various parts of the radioactive sample will be at different distances from the window of the counter, with resulting inaccuracies. The samples should be allowed to dry in a protected place so that no solution is blown from the planchet. Spreading of the solution over the edge of the planchets is prevented by placing the planchets on supports of a smaller diameter. Silvered planchets are to be preferred to copper planchets, since the precipitate of silver iodide is more firmly fixed to the disc and volatilization is prevented. Also, if the radioactive sample is alkaline, as in the case of tissue digests, it might react with the copper to form copper hydroxide, which may increase the absorption in the sample.

Scrupulous care should be exercised in keeping the counting tube and the turntable from becoming contaminated with radioactive substances. It is advisable to "count" the empty turntable occasionally to check for contamination.

The necessity of checking one's pipettes, test tubes, and other glassware should likewise be stressed. Contamination can be avoided. It is mainly a question of good housekeeping and cleanliness.

The Accuracy of the Determination of I^{131} in Urine

These experiments were carried out by adding a known amount of I^{131} to a number of 24-hour urine specimens. The I^{131} and its standard were prepared as for an ordinary radioactive iodine tolerance test. The urine volumes varied between 560 and 1780 ml. and the specific gravities between 1.008—1.028. The I^{131} was determined as described previously. The results are presented in Table 9. A small systematic deviation was observed, the yield being slightly too large in all groups. It is natural that the percentage deviation was greater for very small quantities of I^{131}. The systematic deviation may be due to the fact that samples prepared from urine are somewhat thicker when dried than are those from the standard because of more solid matter in the urine. Thus, these urine samples will be closer to the counter window than are the thinner standard samples. On the other hand, the absorption of beta radiation should be greater within the urine samples and thus tend to decrease the yield. However, other experiments demonstrated that absorption of radiation even within the urine samples could be disregarded.

These yield experiments show that the method for the determination of I^{131} in the urine is very accurate. Of greater importance, however, is the accuracy of the complete radioactive iodine tolerance test as determined from duplicate tests.

Table 9. Experiments on the yield of I^{131} in urine.

Amount of I^{131} added μc	Number of 24 hour urine specimens	Amount of I^{131} found $M \pm \varepsilon (M)$	σ	Difference	Difference in per cent
100	16	101.8 ±0.6	2.3	+1.8	+1.8
50	16	50.6 ±0.5	2.1	+0.6	+1.2
10	16	10.2 ±0.1	0.3	+0.2	+2.0
1	16	1.07±0.02	0.06	+0.07	+7.0

The Accuracy of the Radioactive Iodine Tolerance Test as Determined from Duplicate Tests

In order to determine the accuracy of the I^{131} tolerance test, duplicate tests were carried out in twenty-four patients. In 22 of the patients samples were obtained at 24 and 48 hours, while in two patients complete urines were obtained only for the first 24 hours. The patients were collected among euthyroid and hyperthyroid individuals. They were not especially selected except that only those were used whose regular schedule of treatment was not disturbed by the two tolerance tests.

The 48-hour urinary excretion varied widely between 13.2 and 85.7 per cent. The interval between the two tests was less than 30 days in 21 patients, but in three euthyroid patients the interval was about three months. Clinically there was no apparent change in their thyroid status. The results are presented in Fig. 7.

A comparison between the first and the second test shows that the two tests give the same results. The mean of the differences for the 48-hour urinary excretion was +0.49 per cent of the administered dose with an $\varepsilon (M)$ of ±0.73 per cent. The corresponding result for the first 24-hour excretion was +0.44 ± 0.79 per cent. There was thus no statistically significant difference between the excretion of I^{131} in the first and the second test.

The accuracy of the test σ_i was calculated from the differences (d) between the two tests according to the formula:

$$\sigma_i = \pm \sqrt{\frac{\Sigma d^2}{2n}}$$

(Dahlberg, 1940) where n is the number of patients.

This calculation gives a σ_i of ±2.4 per cent of the administered dose of I^{131} for the 48-hour period. For the 0—24 hour period the σ_i was ±2.7 per cent. The error seemed to be of the same absolute magnitude for both high and low excretions (Fig. 7).

These results demonstrate that the I^{131}-test is reproducible and very accurate. It should be remembered that this σ_i includes all the errors in the radioactive iodine

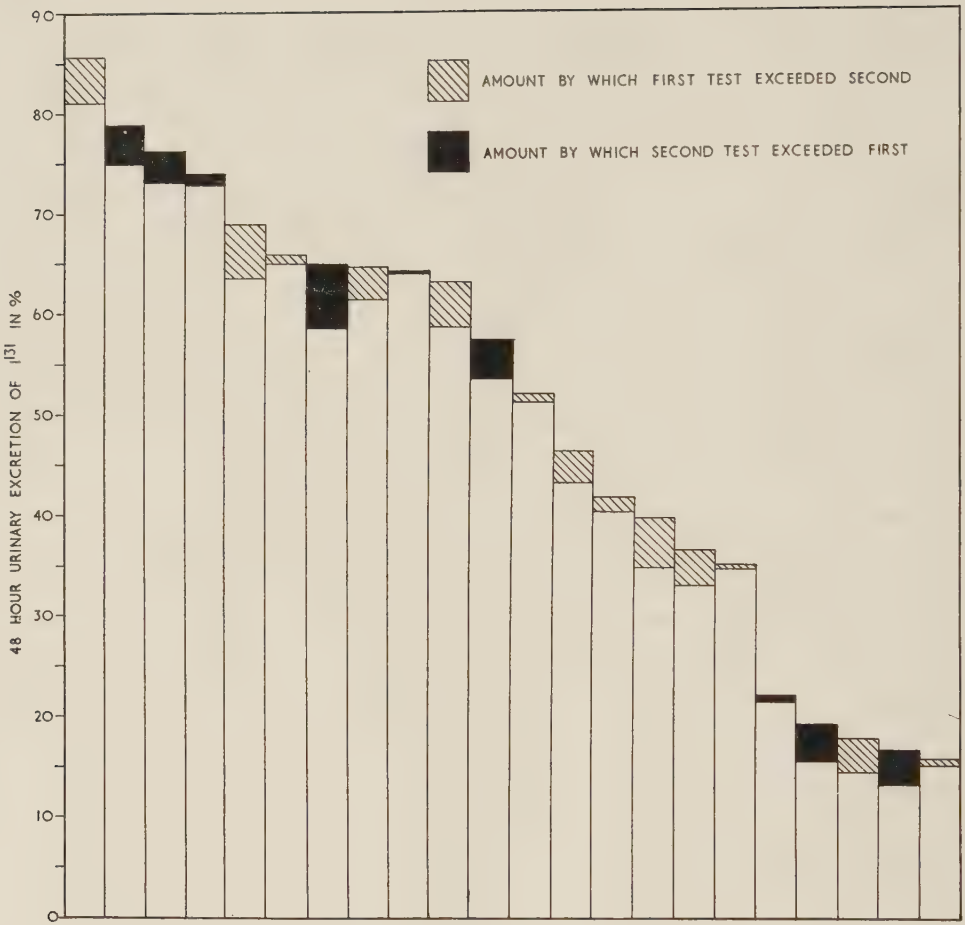

Fig. 7. The repeat reliability of the test. Comparison of the urinary excretion of two tracer doses of I^{131}. Tracer dose constant. Carrier iodine constant.

tolerance test, such as the error in making up the dose of I^{131} and its standard, the error in the measurements of the I^{131} in the urine, the error due to variations in the thyroid activity, the error due to normal variations in the blood iodide concentration, and so forth.

The results show that the daily variations in the thyroid's avidity for iodine are small. Furthermore, they indicate that the thyroid's avidity for iodine does not change appreciably over longer periods of time, provided that there is no apparent change in the clinical state of the thyroid function.

The results also indicate that the thyroid's requirement for iodine stays rather constant for a euthyroid individual. It is evident that the variations of the individual are smaller than are those among different individuals (see. p. 52.)

Other Methods Used in the Present Investigation

Determination of the basal metabolic rate

The Benedict-Roth type of metabolism apparatus was used (Roth, 1922) as were the standards of Aub and Du Bois (1917), or, as they are also called, the Russell Sage Institute Standards.

It is not within the scope of the present paper to deal with the method of the determination of the basal metabolic rate. The reader is referred to the monograph by Du Bois (1936). There are a few points, however, which need to be mentioned.

Naturally the tests were performed under the best possible basal conditions implying a state of mental, physical, and digestive rest. All the tests were carried out in the morning. No food was permitted after twelve midnight. No special diet was used the day before the test. Excessive exercise in the morning before the test was avoided, although exercise could not be completely avoided for out-patients. The patients were asked to lie quietly for half an hour before the test was started. If the patient had not had a previous BMR test he was put through a short dummy test to aquaint him with the procedure. For each test two actual measurements of the basal metabolism were made and the average taken.

In order to eliminate fluctuations in the BMR values due to errors in technique, most of the patients had several tests. The values of BMR's as reported in this paper thus represent averages of several tests. In patients with obvious euthyroidism sometimes not more than one test was performed. In patients with a clear-cut clinical picture of thyrotoxicosis only two or three BMR's were taken. In patients presenting diagnostic problems where it was more important to know the BMR level accurately, four to six tests were usually performed, sometimes more.

The variation of the basal metabolic rate in normal individuals was calculated from the reports in the literature. The results are presented in Table 10. With the exception of the report by Boothby *et al.* (1937) no statistical analysis was carried out in the original papers.

Table 10. **The basal metabolic rate as reported by various investigators.**

Author	Number of subjects	Average BMR	σ
Harris and Benedict (1919)	31	0	7.0
Boothby and Sandiford (1922)	102	+1	5.8
Eggert Møller (1925)	34	—3	6.6
Boothby, Berkson, and Plummer (1937)	547	0	7.0
Total	714	0	6.8

On the basis of the present calculation the following limits were obtained:

$M \pm 2\,\sigma$: +13 to —13 per cent
$M \pm 3\,\sigma$: +20 to —20 per cent

Different investigators have more or less arbitrarily placed the upper limit for normal between +10 and +20 per cent.

Determination of the serum protein-bound iodine

The serum protein-bound iodine was precipitated with Somogyi's reagent (zinc sulphate and sodium hydroxide) as described by Man, Smirnow, Gildea, and Peters (1942). The iodine in the precipitate was determined according to the permanganate acid ashing method developed by Riggs and Man (1940).

The normal limits as calculated from the data of Riggs (1947) were:

$M \pm 2\,\sigma$: 3.5—6.7 μg. per cent
$M \pm 3\,\sigma$: 2.7—7.5 μg. per cent

Riggs considered 3.5—7 μg. per cent as the normal range. The ranges of 3.0—3.5 μg. per cent and 7.0—8.0 μg. per cent were called borderline regions where normal and abnormal were not distinctly separable. Above 8.0 μg. per cent was typical of thyrotoxicosis and below 3.0 μg. per cent characteristic of hypothyroidism.

Determination of the serum cholesterol

The serum cholesterol was determined according to Bloor (1916). The limits for normal variation were obtained from the determinations in 40 normal individuals by Foldes and Murphy (1946 a) (Massachusetts General Hospital) and were as follows:

$M \pm 2\,\sigma$: 121—265 mg. per cent
$M \pm 3\,\sigma$: 85—301 mg. per cent

For other laboratory procedures the current methods at the Massachusetts General Hospital were employed. A table of those methods with the normal values was prepared by Rourke, MacLachlan, and Butler (1946).

Examination of patients

Much emphasis was laid on the clinical examination according to the principles described by Means (1948). The ward patients were first worked up by the resident staff and then seen by the visiting physician. They were also checked by one or

more members of the Thyroid Clinic. All the ward patients, furthermore, were presented and discussed at special thyroid rounds.

The patients in the private wards were examined by at least two members of the Thyroid Clinic.

The out-patients were seen by various members of the Thyroid Clinic. When there was any doubt about the diagnosis the patients were examined and discussed at a special weekly clinic.

Most of the diagnoses were made under the guidance of Drs. J. H. Means and R. W. Rawson.

Chapter IV

CLINICAL MATERIAL

Nomenclature. The term thyrotoxicosis will be used for the disease which is characterized by hyperfunction of the thyroid gland with an increased release of thyroid hormone to the organism. The problem as to whether or not there are other components in this disease entity does not fall within the scope of the present investigation. Hyperthyroidism will be used as a synonym for thyrotoxicosis. In the rare instances where a thyrotoxic state is produced by excessive administration of exogenous thyroid hormone the term thyrotoxicosis factitia will be employed.

The term Graves' disease has the advantage that it is comprehensive enough to include all varieties of cases which are considered to have a common etiology. It has the disadvantage of not describing the functional state of the thyroid. Though the majority of cases of Graves' disease are characterized by hyperthyroidism there are certain cases associated with euthyroidism. To be entirely clear the term Graves' disease should be followed by a qualifying expression regarding thyroid function. Therefore, in this study of the differentiation of disturbances of thyroid function the term Graves' disease will be avoided when other adequate terms can be employed. The term hyperophthalmopathic Graves' disease (Means, 1948) will be used for the form of Graves' disease in which the eye symptoms dominate the clinical picture and thyrotoxicosis is absent or minimal.

Classification of thyroid disorders. There is no ideal way of classifying thyroid disorders. Whether the classification is based on etiology, pathology, or physiology there will be overlapping. For the purpose of studying different methods of evaluating thyroid function, the physiologic approach seems to be most adequate. Therefore, in this paper thyroid disorders will be divided into groups with hyperfunction, normal function, and hypofunction. From the clinical point of view this will have the disadvantage that certain clinical entities, such as chronic thyroiditis, will have to be discussed in different places depending upon the functional state of the gland. However, similar disadvantages have to be faced whatever classification is used.

Composition of the clinical material. The present investigation is based on a study of 110 normal subjects and 385 patients with a variety of diseases, primarily thyroid

Table 11. Clinical material.

Diagnosis	Thyrotoxicosis suspected but excluded	Total thyroidectomy	Nontoxic goiter with diagnostic problems	Totals		Case numbers
Euthyroid					282	
Normal individuals	0	0	0	110		N 1—N 110
Nontoxic goiter without diagnostic problems	0	0	0	41		188—228
Carcinoma of the thyroid						
1. Proved	2	4	0	25		268—292
2. Suspected	0	2	0	2		293—294
Chronic thyroiditis	2	1	0	11		295—305
Renal disease	0	0	0	10		338—347
Diseases simulating thyrotoxicosis						
1. Hyperophthalmopathic Graves' disease	4	0	0	4		348—351
2. Unilateral exophthalmos	2	0	2	2		229—230
3. Cardiovascular disease	16	0	9	20		231—239, 352—362
4. Anxiety neurosis	12	0	10	22		240—249, 363—374
5. Diseases of the blood and reticuloendothelial system	3	0	3	10		250—252, 375—381
6. Nontoxic goiter	7	0	7	7		253—259
7. Miscellaneous diseases	12	0	8	12		260—267, 382—385
Various patients used for special studies	0	0	0	6		332—337
Hyperthyroid					187	
Thyrotoxicosis						
1. Without diagnostic problems	0	0	0	94		1— 94
2. With diagnostic problems	0	0	0	81		95—175
Thyrotoxicosis factitia	3	0	0	3		176—178
Thyrotoxic patients used for special studies during the course of treatment	0	0	0	4		179—182
Thyrotoxicosis suspected but not proved	0	0	0	5		183—187
Hypothyroid					26 [1]	
Myxedema	0	1	0	24 [1]		306—329
Hypothyroidism due to thiocyanate	0	0	0	2		330—331
Totals	63	8	39 [2]		495	

[1] Cases 278 and 279 with carcinoma of the thyroid were also studied in a hypothyroid state but are not included in this total.

[2] Cases 229—267.

disorders. These 385 patients include those discussed in earlier papers (SKANSE 1948 a, 1948 b), and two cases of thyrotoxicosis factitia reported by SKANSE and RIGGS (1948). Furthermore, they include 39 of the 52 patients in the paper of MCARTHUR *et al.* (1948). Of the 13 patients excluded, 12 patients were from the group McArthur *et al.* classified as nonthyrotoxic and were omitted for the following reasons: inadequate follow-up in patients in whom thyrotoxicosis was suspected (5 cases), no clinical data available to the present author (3 cases), thyroid medication at the time of study (1 case), cholecystogram at the time of study (1 case), and carrier iodine more than 100 μg. (2 cases). One of the patients from their group of thyrotoxic cases could not be included because of lack of clinical data. Three patients classified by McArthur *et al.* as nonthyrotoxic were later proved to have hyperthyroidism and are in the present study classified as such.

Table 11 gives a survey of the clinical material arranged according to the functional state of the thyroid gland. The division of patients with nontoxic goiter and patients with thyrotoxicosis into subgroups will be discussed in the text. Patients in whom the diagnosis of thyrotoxicosis was neither proved nor disproved are listed under hyperthyroidism for convenience.

The number of patients in whom thyrotoxicosis was suspected but finally excluded is necessarily arbitrary and dependent upon the physicians' judgment. This category is included to demonstrate in which types of patients the possibility of thyrotoxicosis had particularly to be considered. Furthermore, it indicates that thyrotoxicosis was not seriously suspected in all patients that are listed under the heading of diseases that may simulate thyrotoxicosis.

For identification of the case numbers the corresponding numbers of the hospital records are listed on pp. 181—182.

Chapter V

THE URINARY EXCRETION OF RADIOACTIVE IODINE (I^{131}) IN NORMAL INDIVIDUALS AND IN TOTALLY THYROIDECTOMIZED PATIENTS

Normal individuals

The variation of a test among normal individuals naturally is dependent upon the criteria used for the selection of the normals. For a laboratory test that is to be used in clinical medicine the criteria of normality should be chosen to serve practical purposes. Therefore, in this study an individual was considered normal as far as thyroid and renal functions were concerned when:

1. there were no symptoms of thyroid or renal disease in the case history,
2. there was no medication with thyroid tablets or drugs containing iodine during the previous six months,
3. there was no administration of contrast media containing iodine used for cholecystograms or pyelograms during the previous year, or lipiodol at any time,
4. the ordinary physical examination revealed no signs of disease which might affect thyroid or renal function.

The iodine intake probably was comparatively high, as Boston is located by the sea, and sea food is a regular part of the diet.

The basal metabolic rate was not determined regularly. Single determinations were considered of little value, and multiple tests could not be arranged as they interfered too much with the regular work of the volunteers. An exception was a group of sixteen individuals selected among those with the highest and the lowest excretion of radioactive iodine. Their basal metabolic rates were within ± 15 per cent.

The normal individuals were collected among employees of the Massachusetts General Hospital.

There were 110 subjects, 62 women and 48 men. More women than men were studied, as it was considered important to define carefully the variations of the radioactive iodine excretion in this sex in which thyrotoxicosis appears more frequently.

For the purpose of studying the influence of age on the test, the normal subjects were divided into three groups: 15—34, 35—54, and 55—74 years, or young, middle-

Table 12. The urinary excretion of radioactive iodine of normal men and women. difference $\varepsilon(D)$, and

Age group	Number	Urinary excretion of Men					
		0—24 hours		24—48 hours		Total in 48 hours	
		$M \pm \varepsilon(M)$	σ	$M \pm \varepsilon(M)$	σ	$M \pm \varepsilon(M)$	σ
15—34 years	17	63.3±1.9	7.8	5.1±0.5	1.9	68.3±2.1	8.8
35—54 »	15	58.5±2.0	7.9	5.2±0.5	2.1	63.7±2.1	8.2
55—74 »	16	59.2±1.4	5.6	5.2±0.4	1.6	64.4±1.3	5.1
All ages	48	60.4±1.1	7.3	5.2±0.3	1.8	65.6±1.1	7.7

[1] One subject was actually 76 years old.

aged, and elderly individuals. This division was also chosen for physiologic reasons, as it is conceivable that the thyroid function might change during the climacterium. The middle group will cover that period.

The results of the radioactive iodine tolerance test in normal individuals are presented in Table 12. No statistical differences could be demonstrated between the sexes or among the different age groups in either sex. Therefore, all the normal individuals were taken together for the calculation of the normal variation. The results are given in Table 13. The average 48-hour urinary excretion in normal individuals was found to be 65.9 ± 0.7 per cent. The corresponding values for the 0—24 hour period and the 24—48 hour period were 60.6 ± 0.7 per cent and 5.3 ± 0.2 per cent respectively. In using this test for the diagnosis of thyrotoxicosis it is necessary that the mean of the normals differ significantly from the mean of thyrotoxic patients. This is not enough, however. To estimate the result of the test in the individual patient, the variation of the mean of the normals must also be considered. In Table 13 the limits for normal variation are given for various degrees

Table 13. **The normal variation in the urinary excretion of radioactive iodine. Mean (M), standard error of the mean $\varepsilon(M)$, and standard deviation (σ).**

Urinary excretion of I^{131}	Number of subjects	$M \pm \varepsilon(M)$ per cent	σ	Limits for the range of normal variation			Observed range of variation per cent
				$M \pm 2\ \sigma$ per cent	$M \pm 2.5\ \sigma$ per cent	$M \pm 3\ \sigma$ per cent	
0—24 hours	110	60.6±0.7	6.9	46.8—74.4	43.3—77.9	39.8—81.3	47.2—79.6
24—48 »	110	5.3±0.2	2.1	1.1— 9.5	0 —10.6	0 —11.6	0.6—13.1[1]
Total in 48 hours	110	65.9±0.7	7.3	51.3—80.5	47.6—84.2	44.0—87.8	52.6—85.7

[1] Two values > 11.6 per cent.

Mean (M), standard error of the mean $\varepsilon(M)$, standard error of the standard deviation (σ).

radioactive iodine in per cent

Number	Women						Difference between men and women
	0—24 hours		24—48 hours		Total in 48 hours		
	$M \pm \varepsilon(M)$	σ	$M \pm \varepsilon(M)$	σ	$M \pm \varepsilon(M)$	σ	$D \pm \varepsilon(D)$
20	60.7±1.4	6.1	4.9±0.5	2.4	65.7±1.5	6.7	2.6±2.6
21	62.1±1.6	7.3	5.2±0.6	2.8	67.3±1.7	7.6	—3.6±2.7
21[1]	59.6±1.5	6.7	5.9±0.4	1.6	65.5±1.5	6.8	—1.1±2.0
62	60.8±0.8	6.7	5.3±0.3	2.3	66.2±0.9	7.0	—0.6±1.4

of probability. The range of $M \pm 3\sigma$[1] was chosen as normal. Values outside these limits were considered as definitely abnormal. A more narrow range such as $M \pm 2.5\sigma$ or $M \pm 2\sigma$ could have been chosen also. The probability that a normal patient would fall outside of the adopted normal limits then increases, whereas 99.7 per cent of normal subjects fall within the range of $M \pm 3\sigma$. The advantage of using the $\pm 3\sigma$ limit is apparent provided that it is feasible in clinical work.

It may be pointed out that no systematic attempt has been made previously to determine the normal limits for the urinary excretion of radioactive iodine in healthy individuals. It is of interest, however, to compare the results obtained here with some scattered data reported in the literature (Table 4, p. 18). Hertz and Roberts (1942) observed 62 per cent excretion in one normal individual. Keating *et al.* (1947) found values between 60—70 per cent in four normal subjects.

More is known about euthyroid individuals collected among hospital patients without known thyroid disorder. Quimby and McCune (1947) found in six children a 48-hour excretion between 62 and 79 per cent. Skanse (1948 b) observed in 15 euthyroid patients an average excretion of 66.6 per cent with an observed range of 52.7 to 84.1 per cent. These latter values are almost identical to those now observed in healthy subjects. It is of great importance for the usefulness of the test that euthyroid patients with a variety of nonthyroid diseases give values that do not differ from those observed in healthy subjects. Werner *et al.* (1948) found in 30 euthyroid patients somewhat lower excretion values and a wider range of variation than has been observed in the present study. The reason for this is not absolutely clear, but it might have been due to the use of carrier-free radioactive iodine. In the present study carrier-free I^{131} was avoided for reasons previously mentioned.

Totally thyroidectomized patients

In order to use the urinary excretion of I^{131} as a measure of thyroid function it was necessary to know how ingested I^{131} was handled by other tissues of the body

[1] M = normal mean. σ = standard deviation.

Table 14. The urinary excretion of I^{131} in totally thyroidectomized patients.

Case number	Urinary excretion of I^{131} in per cent				Remarks
	0—24 hours	24—48 hours	48—72 hours	Total	
287	90.0	8.4	2.9	101.3	Euthyroid
292	80.5	14.5	—	95.0	»
293	90.6	5.3	3.1	99.0	»
294	85.0	11.9	2.7	99.6	»
297	78.3	15.0	—	93.3	»
278	66.0	30.0	5.0	101.0	Hypothyroid
279	76.6	18.1	3.2	97.9	»
310	77.9	18.1	—	96.0	»

than the thyroid. In normal individuals on the average about 35 per cent of the I^{131} was either retained by the body or excreted by routes other than the kidneys. At least a large part of this residual I^{131} was retained by the thyroid. It was considered likely that radioactive iodine tolerance tests in athyreotic individuals would provide most of the necessary information about extrathyroidal metabolism of I^{131}. Such studies might also provide information about the amount of I^{131} that was collected by the thyroid.

The urinary excretion of I^{131} was determined in eight patients, in whom total thyroidectomy had been performed. Five of the patients were studied shortly after the thyroidectomy when they still were in a euthyroid state, while three patients were myxedematous.

The results of the I^{131}-test are presented in Table 14. The urinary excretion of I^{131} varied between 93.3 and 101.3 per cent with an average of 97.9 per cent. The lowest values were obtained in those patients whose urine collections were made for only 48 hours. The excretion of I^{131} in these patients would probably have been still closer to 100 per cent, had the urine been collected for 72 hours. The results demonstrate that essentially all the I^{131} is excreted in the urine in totally thyroidectomized patients. It may be concluded indirectly that the fecal excretion of I^{131} is very low. This observation corroborates the findings of Hamilton and Soley (1939) obtained from direct analyses of feces. Furthermore, other routes of iodine elimination seem to be of little significance for the I^{131}-test. It is also apparent that tissues other than the thyroid collect very little, if any, I^{131}. From the practical point of view it may be stated that the thyroid and the kidneys are the only competitors for I^{131}. The results indicate that the urinary excretion of I^{131} can be used as an indirect measure of the thyroid's capacity to collect I^{131}.

In summary, the 48-hour urinary excretion of I^{131} in 110 normal individuals was found to be 65.9 ± 0.7 per cent. No difference was observed between men and women

or among various age groups. The normal range ($\pm 3\,\sigma$ of the normal mean) for the urinary excretion of I^{131} was 44.0—87.8 per cent for 48 hours, 39.9—81.3 per cent for the 0—24 hour period, and 0—11.6 per cent for the 24—48 hour period. No systematic investigation of the urinary excretion of radioactive iodine in healthy subjects has been reported previously. In totally thyroidectomized patients there was an almost complete excretion of I^{131} in the urine.

Chapter VI

A COMPARISON OF THE RADIOACTIVE IODINE TOLERANCE TEST WITH OTHER LABORATORY TESTS IN PATIENTS WITH THYROID DISEASE

Hyperthyroidism

The fully developed picture of thyrotoxicosis is very characteristic and presents no problem in diagnosis. The combination of a number of symptoms and signs makes for easy clinical recognition. There is, however, no symptom or sign which is pathognomonic of thyrotoxicosis. Few diseases present such a great variation in the clinical picture. Almost all the characteristic symptoms and signs may be missing, and yet the disease may turn out to be thyrotoxicosis. Therefore, it is necessary to define the criteria for its diagnosis. In this study, whenever necessary, the response to specific treatment with disappearance of the symptoms and signs was used as the basis for the final diagnosis. In particular the following objective criteria were considered:

1. gain of weight
2. fall of pulse rate
3. fall of basal metabolic rate

In a number of patients additional support for the diagnosis was obtained from preoperative response to iodine or antithyroid drugs, and from the anatomic changes observed in the glands removed at operation. However, in most patients the finding of hyperplasia could not be used in support of the diagnosis because of the use of thiourea derivatives preoperatively.

It should be emphasized that the results of the radioactive iodine tolerance test and the values of the serum protein-bound iodine were not allowed to influence the diagnostic classification. However, the results of these tests did play an important rôle in the later handling of the patient.

Patients with thyrotoxicosis were divided into two subgroups:

a) Patients in whom the clinical diagnosis of thyrotoxicosis was apparent at the time of study.

b) Patients in whom the clinical diagnosis was not apparent at the time of study but whose subsequent studies, clinical course, and response to treatment served to establish the diagnosis of thyrotoxicosis with reasonable certainty.

This division is necessarily rather arbitrary. When the second group is discussed in a later chapter, it will be apparent that these patients did present real diagnostic problems. The division was made to facilitate the discussion of the diagnosis of thyrotoxicosis in Chapter VIII. Naturally this division does not interfere with the results.

The patients with thyrotoxicosis were not entirely unselected. There is undoubtedly an overrepresentation of atypical and complicated cases. In the first place, a number of the patients were sent to the hospital just because they were atypical or complicated. Secondly, it was not considered necessary to study every patient with clinically obvious thyrotoxicosis. Thirdly, in evaluating the radioactive iodine tolerance test in the diagnosis of thyrotoxicosis, atypical cases were especially collected. In unselected patients with thyrotoxicosis diagnostic problems will not arise as frequently as in this study.

1. Thyrotoxicosis

a) *Patients in whom the clinical diagnosis of thyrotoxicosis was apparent at the time of study.*

This group of cases consisted of 94 patients (Cases 1—94), in whom the diagnosis of thyrotoxicosis could be made from the history, the clinical findings, and the basal metabolic rate. The age and sex distribution is given in Table 15. The age varied between 12 and 75 years. In 18 of the patients the thyrotoxicosis was recurrent, while in the rest of the group there was no known earlier episode of thyrotoxicosis. Eighty-six patients were untreated. Eight patients had received unsuccessful or incomplete treatment with iodine, thiouracil, or radioactive iodine prior to this study.

The frequency of the most important symptoms and signs is given in Table 16. It can be seen that this group of patients represented fairly typical cases of thyro-

Table 15. **Patients with unequivocal thyrotoxicosis distributed according to age and sex.**

Age, years	Women	Men
10—19	5	0
20—29	18	1
30—39	16	3
40—49	18	6
50—59	16	3
60—69	6	1
70—79	0	1
Total	79	15

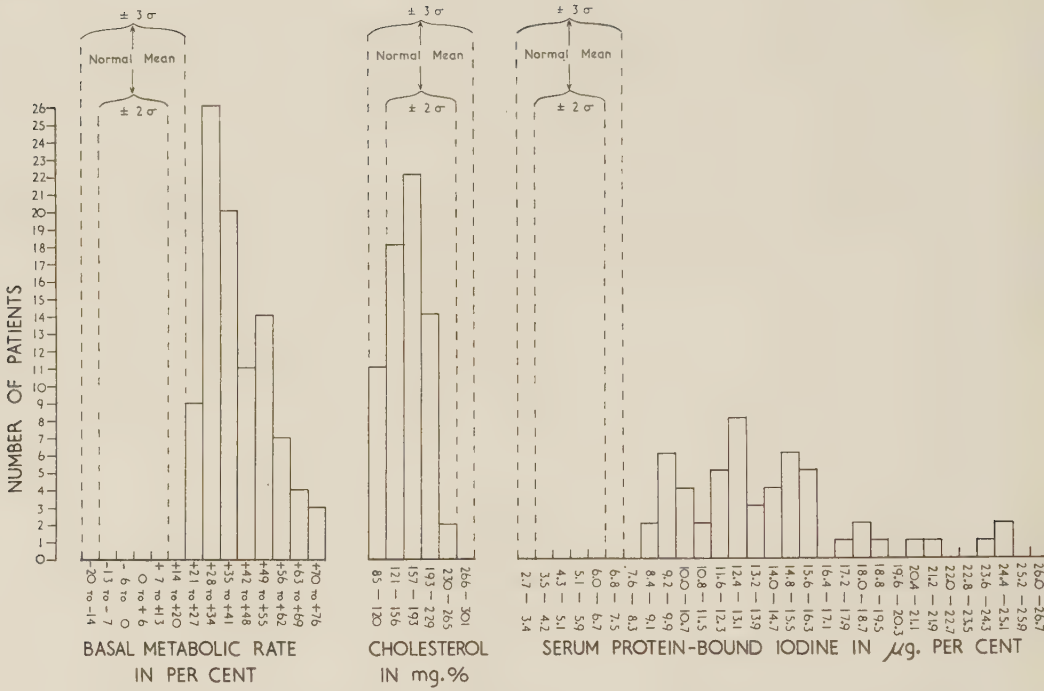

Fig. 8. The basal metabolic rate, the serum cholesterol, and the serum protein-bound iodine in patients with clinically apparent thyrotoxicosis.

toxicosis. Such cardinal signs as goiter, tachycardia, and tremor were present in a high percentage of the cases. It may be noted that exophthalmos appeared in only 51 per cent of the cases. In 17 patients the thyrotoxicosis was complicated in several ways such as: congestive failure (6 cases), coronary heart disease (2 cases), rheumatoid arthritis (4 cases), diabetes mellitus (2 cases), psychosis (2 cases), bronchial asthma (1 case), and Miculicz' syndrome (1 case). None of the patients was known to have renal disease. Despite these complications the diagnosis of thyrotoxicosis was never doubted. Treatment included subtotal thyroidectomy (38 cases), radioactive iodine (53 cases), and antithyroid drugs (3 cases). The results were satisfactory in 87 patients, while in seven cases the follow-up was inadequate.

The results of the determinations of basal metabolic rate, serum cholesterol, serum protein-bound iodine, and urinary excretion of radioactive iodine are presented graphically in Fig. 8 and Fig. 9.

The basal metabolic rate varied between +21 and +74 per cent with an average of +42 per cent. Patients with normal basal metabolic rates (within ±20 per cent) were referred to the group of patients with diagnostic problems. As can be seen from the distribution of the basal metabolic rates, there was considerable variation in the severity of the disease. The majority of the patients, however, represented

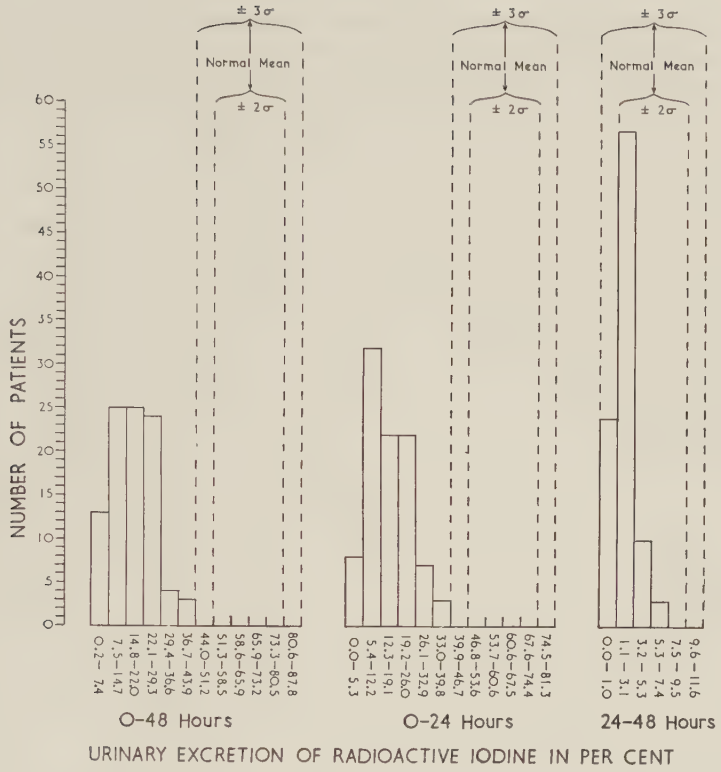

Fig. 9. The urinary excretion of I^{131} in patients with clinically apparent thyrotoxicosis.

moderately severe cases. A relatively large number had mild thyrotoxicosis, and only a few had severe disease.

The serum cholesterol was determined in 67 cases. Fifty-six cases were within the range of $\pm 2\,\sigma$ of the normal mean, and all cases within $\pm 3\,\sigma$ of the normal mean. Thus, in no case was the serum cholesterol definitely below normal, although most of the values were less than the average of the normals. An isolated serum cholesterol determination, therefore, cannot be used as a diagnostic aid in thyrotoxicosis.

The serum protein-bound iodine was determined in 57 cases. It varied between 8.7 μg. per cent and 36.1 μg. per cent with an average of 14.9 μg. per cent. Thus, the serum protein-bound iodine was constantly elevated in this group of patients with fully-developed thyrotoxicosis.

The total 48-hour urinary excretion of I^{131} varied between 1.9 per cent and 38.6 per cent with an average of 17.4 $\pm$ 0.9 per cent. All the values in this group of 94 cases of apparent thyrotoxicosis fell more than $3\,\sigma$ below the normal mean. The excretion of I^{131} during the 0—24 hour period averaged 15.5 $\pm$ 0.8 per cent. It was

Table 16. The occurrence of the more important symptoms and signs in 94 patients with clinically apparent thyrotoxicosis.

	Number of cases	Per cent
Symptoms		
Weight loss	80	85
Increased appetite	64	68
Intolerance to heat	69	73
Sweating	66	70
Fatigue	72	77
Palpitation	78	83
Swelling of the neck	48	51
Prominence of the eyes	38	40
Nervousness	87	93
Tremor	73	78
Signs		
Goiter		
diffuse 78		
nodular 10	88	94
$1\frac{1}{2} \times$ normal size 9		
$> 1\frac{1}{2} \times$ » » 79		
Warm and moist skin	80	85
Tremor	90	96
Exophthalmos	48	51
Other eye signs	65	69
Pulse rate ≥ 90	81	86
» » ≥ 80	91	97
Auricular fibrillation	11	12
BMR $>$ + 20 per cent	94	100

also invariably less than normal. This finding suggests that the 24-hour excretion of I^{131} can be used as well as the 48-hour excretion in the diagnosis of thyrotoxicosis. The values for the 24 –48 hour excretion fell within the normal range, although the average of 1.9 $\pm$ 0.1 per cent was less than the normal mean of 5.3 $\pm$ 0.2 per cent.

There was no indication that the size of the thyroid gland affected the urinary excretion of I^{131}. Very low excretion values were found as often in patients with small goiters as in patients with large goiters.

It is of interest to compare the results of the radioactive iodine tolerance test in this group of thyrotoxic patients with results from comparable thyrotoxic patients reported in the literature. (Table 4, p. 18). Keating *et al.* (1947) observed in sixteen thyrotoxic patients somewhat higher excretion values and a greater variability. Two of the patients gave values in the same range as found in the euthyroid patients. No explanation for this was found. The results reported by Skanse (1948 a,

1948 b) in 25 thyrotoxic patients also agree well with the present findings. It should be remembered, however, that the patients presented here include some of the same patients as in the preliminary reports by SKANSE (1948 a, 1948 b). WERNER *et al.* (1948) obtained similar values in 28 thyrotoxic patients although the variation was less than in the present study.

As was stated previously, the present group of thyrotoxic patients did not present any difficult diagnostic problems. They were studied in order to observe the behavior of the radioactive iodine tolerance test in clinically apparent thyrotoxicosis. It was expected that the thyroid gland in thyrotoxicosis would have an increased avidity for iodine and consequently result in a lower than normal urinary excretion of radioactive iodine. The results demonstrate that the urinary excretion of I^{131} is consistently decreased in clinically well-defined thyrotoxicosis. This is essential for a test that is to be used for diagnostic purposes. The results also suggest that the radioactive iodine tolerance test might be used as a diagnostic aid in patients with thyrotoxicosis in whom the true basal metabolic rate cannot be obtained.

In conclusion, the urinary excretion of I^{131} in 24 hours and 48 hours was invariably less than normal in 94 patients with clinically apparent thyrotoxicosis and elevated basal metabolic rate. The serum protein-bound iodine, determined in fifty-seven patients, was elevated in all patients. The serum cholesterol, determined in sixty-seven patients, was within normal limits in all patients. The radioactive iodine tolerance test and the serum protein-bound iodine thus fulfill an essential requirement for a reliable diagnostic test in giving consistent results in the fully-developed disease. On the other hand, the determination of serum cholesterol does not appear to contribute to the diagnosis of thyrotoxicosis.

b) *Patients in whom the clinical diagnosis of thyrotoxicosis was not established at the time of study.*

This group consisted of 81 patients (Cases 95—175). The age and sex distribution is given in Table 17. The larger number of older patients in this group, as compared to the previous group, is not unexpected. Diagnostic problems are more likely to arise in elderly patients where the clinical picture of thyrotoxicosis is more often obscured by complicating diseases. In 11 of the patients the thyrotoxicosis was recurrent. In seven patients it was caused by a hyperfunctioning single adenoma.

The occurrence of the more important symptoms and signs is given in Table 18. A more detailed discussion of the clinical picture will appear in Chapter VIII on the diagnosis of thyrotoxicosis. A comparison between this group and the one with clinically unequivocal thyrotoxicosis shows, as might be expected, that the frequency of the typical symptoms and signs is much lower in the present group. In 35 of the patients the thyrotoxicosis was complicated by other diseases, predominantly cardiovascular. In a number of these patients such complicating diseases obscured the clinical picture sufficiently to cause diagnostic difficulties. None of

Table 17. Thyrotoxic patients with diagnostic problems distributed according to age and sex.

Age, years	Women	Men
10—19	0	0
20—29	11	1
30—39	11	1
40—49	10	4
50—59	23	4
60—69	8	4
70—79	3	1
Total	66	15

Table 18. The occurrence of the more important symptoms and signs in 81 patients with clinically uncertain thyrotoxicosis.

	Number of cases	Per cent
Symptoms		
Weight loss	52	64
Increased appetite	31	38
Intolerance to heat	37	46
Sweating	38	47
Fatigue	53	65
Palpitation	47	58
Swelling of the neck	26	32
Prominence of the eyes	11	14
Nervousness	60	74
Tremor	38	47
Signs		
Goiter		
diffuse 39		
nodular 27	66	81
$1\frac{1}{2}\times$ normal size 25		
$>1\frac{1}{2}\times$ » » 41		
Warm and moist skin	35	43
Warm but not moist skin	19	23
Tremor	61	75
Exophthalmos	11	14
Other eye signs	34	42
Pulse rate ≥ 90	47	58
» » ≥ 80	73	90
Auricular fibrillation	5	6
BMR $\leq +20$ per cent	39	48

the patients had known renal disease. The response to treatment (subtotal thyroidectomy, 34 cases; radioactive iodine, 25 cases; potassium iodide, 10 cases; antithyroid drugs, 10 cases) was satisfactory in all cases except that one patient died from coronary thrombosis before the final effect of treatment could be evaluated. There were spontaneous remissons in two patients.

The results of the determinations of basal metabolic rate, serum cholesterol, serum protein-bound iodine, and urinary excretion of radioactive iodine are presented graphically in Fig. 10. and Fig. 11.

The results of the tests in four patients (Cases 96, 101, 135, and 170) are excluded from Fig. 10 and Fig. 11 because of previous administration of contrast media containing iodine which may influence the tests. The results in these four patients will, however, be discussed in Chapter VIII on the diagnosis of thyrotoxicosis.

The basal metabolic rate for the 77 patients varied between —6 and +97 per cent, with an average of +23 per cent.[1] No less than 38 patients (49 per cent) had basal metabolic rates within $\pm 3\,\sigma$ of the normal mean (within ± 20 per cent). Twenty patients (26 per cent) were within $\pm 2\,\sigma$ of the normal mean. There are probably several reasons for normal basal metabolic rates in thyrotoxicosis. In a number of patients with a normal BMR it was observed that the BMR dropped to and stayed at subnormal values when they were freed of their thyrotoxicosis, but they developed no symptoms or signs of myxedema. It is likely that the BMR rose during the development of thyrotoxicosis but not enough to produce a value above the normal limit.

The BMR may be looked upon as a means of measuring the total impact of thyroid hormone on the cells of the whole body. It is possible that there is a good deal of variation among the organs in their sensitivity to thyroid hormone. When thyrotoxic symptoms from one organ system of the body do appear, it may not be enough to raise the metabolism above normal limits. This explanation of variations in sensitivity of the "end-organs" would also explain the often bizarre combinations of symptoms and signs in certain patients.

The BMR was above +40 per cent in only nine patients. Five of these patients were included in this group because of atypical clinical findings, and four patients because of the presence of complicating diseases which may raise the BMR.

The basal metabolic rates obtained demonstrate that this test is not sensitive enough to detect all mild and atypical cases of thyrotoxicosis.

The serum cholesterol was determined in 59 cases, but four values (all normal) were excluded for reasons given above. Fifty-three cases were within $\pm 3\,\sigma$ of the normal mean and 49 within $\pm 2\,\sigma$ of the normal mean. In one patient the cholesterol was above normal, and only one value was definitely below normal. These results are a further indication that a single determination of the serum cholesterol is of no aid in the diagnosis of thyrotoxicosis. This does not imply that the rise in cholesterol during treatment cannot be used as additional support for the diagnosis.

The serum protein-bound iodine was determined in 59 patients. Three patients

[1] The four patients excluded from the calculation had BMR's of +26, +27, +28, and +19 per cent.

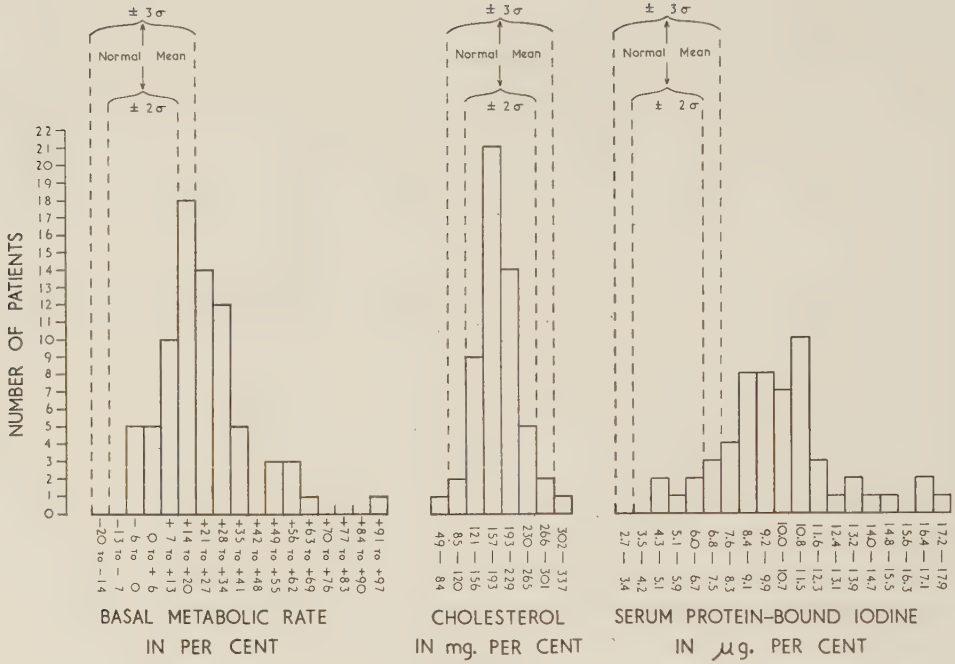

Fig. 10. The basal metabolic rate, the serum cholesterol, and the serum protein-bound iodine in patients with thyrotoxicosis, in whom the diagnosis was not established at the time of study.

who had recent cholecystograms are excluded from Fig. 10 and from the following calculations as cholecystograms are known to cause spurious elevations of the serum protein-bound iodine. The serum protein-bound iodine varied between 4.7 μg. per cent and 17.9 μg. per cent with an average of 10.1 μg. per cent. In 48 patients it was more than 3 σ above the normal mean and in 51 patients more than 2 σ above the normal mean. The frequency of normal serum protein-bound iodine values observed in the whole group of thyrotoxic patients (8 cases out of 113) is consistent with the results reported by Riggs (1947) and Winkler (1947). In fact, the results reported here may be even more significant as the number of patients with mild and atypical thyrotoxicosis is probably larger in the present study.

The radioactive iodine tolerance test was carried out in all patients, but four patients (Cases 96, 101, 135, and 170), who had had recent cholecystograms are excluded from Fig. 11 and the following calculations. In two patients urine was collected for only 24 hours. The 48-hour excretion of I^{131} in 75 patients varied between 8.4 per cent and 66.1 per cent with an average of 29.0 $\pm$ 1.3 per cent. As compared to an average excretion of 17.4 $\pm$ 0.9 per cent for patients with unequivocal thyrotoxicosis, the excretion of I^{131} in this group of patients is definitely higher. This is not surprising in view of the fact that the present group includes a large number of patients with mild thyrotoxicosis. In 71 patients the 48-hour excretion was more

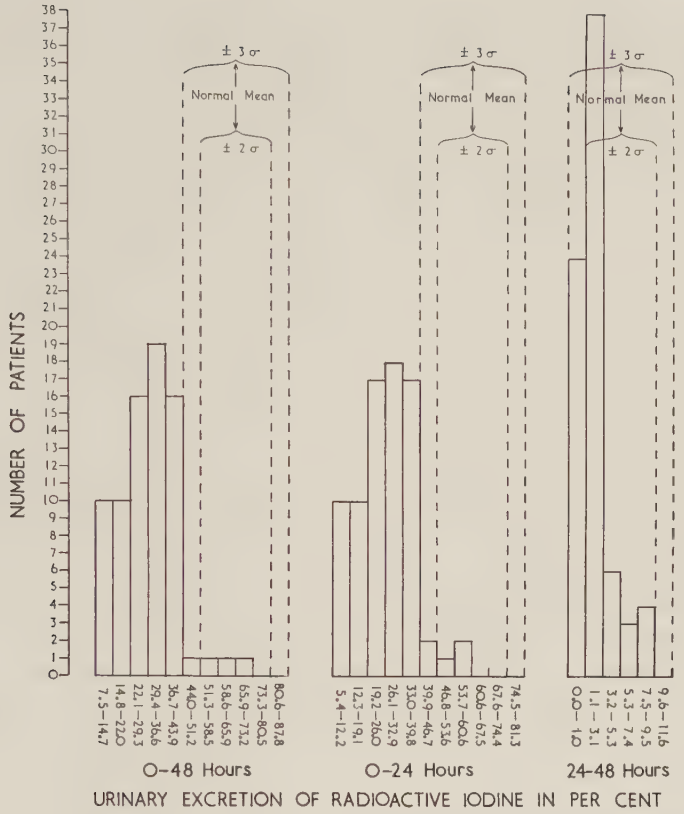

Fig. 11. The urinary excretion of I^{131} in patients with thyrotoxicosis, in whom the diagnosis was not established at the time of study.

than 3 σ below the normal mean and in 72 patients more than 2 σ below the normal mean. Thus, in three patients the 48-hour excretion was definitely normal. These cases, which must be considered as failures from the diagnostic point of view, are discussed in detail in Chapter VIII (p. 126).

The results of the 24-hour excretion of I^{131} were similar to those for 48 hours. The mean was 26.6 $\pm$ 1.2 per cent. In 72 patients the 24-hour excretion was more than 3 σ below the normal mean and in 74 patients more than 2 σ below the normal mean. Three patients (the same three as in the 48-hour interval) gave definitely normal excretion values. The results indicate that the 24-hour urinary excretion of I^{131} may be as reliable as the 48-hour excretion in detecting thyroid hyperfunction.

All the excretion figures for the 24—48 hour period were in the normal range although the average of 2.2 $\pm$ 0.2 per cent was less than the normal average of 5.3 $\pm$ 0.2 per cent.

This group of patients includes a great number of atypical, mild and complicated

cases of thyrotoxicosis. The laboratory methods, therefore, were put to a real test. As might have been expected, none of them completely stood that test. There is no doubt that the BMR is insufficiently sensitive for the diagnosis of thyrotoxicosis, though it is an excellent screening test. An elevated BMR is strong support for the diagnosis when other causes of elevated BMR's can be excluded. A normal BMR cannot be used to exclude thyrotoxicosis. This study has demonstrated that thyrotoxicosis with a normal BMR is no rarity although the frequency cannot be estimated from the present data. The determination of the serum protein-bound iodine is a much more sensitive method of demonstrating the disturbed thyroid function in thyrotoxicosis. The radioactive iodine tolerance test may be still more sensitive. Like other laboratory methods it is not infallible, however. The relative merits of the two last methods will be discussed in Chapter XI.

As a large part of the present clinical material was especially selected to study laboratory methods in thyrotoxicosis, there is no good reason for putting the two groups of thyrotoxicosis together in order to obtain a single larger group for the statistical calculations. Such an approach would not indicate the behavior of the tests in unselected cases of thyrotoxicosis. The results of the laboratory tests in these two groups demonstrate that the values for any group of patients with thyrotoxicosis will depend to a large extent upon the relative proportions of severe, mild, atypical, and complicated cases. From the clinical point of view it is more important to know the sensitivity and reliability of the diagnostic tests under the most unfavorable conditions. The present group of patients with thyrotoxicosis undoubtedly presents some of the most difficult problems that arise in making the diagnosis of thyrotoxicosis. *Under such circumstances the basal metabolic rate indicated thyrotoxicosis in 51 per cent of the cases, the serum protein-bound iodine in 86 per cent, and the radioactive iodine tolerance test in 95 per cent.* Thus, it appears that the radioactive iodine tolerance test may be the most sensitive laboratory method for detecting thyrotoxicosis. Whether it is the best available method cannot be determined until the specificity of the test has been investigated in patients with diseases that simulate thyrotoxicosis. The results of such a study will be presented in Chapter IX.

2. Thyrotoxicosis factitia

The term "thyrotoxicosis factitia" applies to the morbid condition occurring when a thyrotoxic state is produced by an excessive intake of thyroid. Other terms that have been used are alimentary thyrotoxicosis and self-induced thyrotoxicosis. It may also be called exogenous thyrotoxicosis in order to distinguish it from the ordinary endogenous thyrotoxicosis.

In the present investigation three patients with thyrotoxicosis factitia were studied. In two of the patients the diagnosis was definitely established later, while in the third patient circumstantial evidence strongly favored the diagnosis.

Table 19. **The results of laboratory tests in thyrotoxicosis factitia.**

Case number	Date	BMR per cent	Cholesterol mg per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent		
					0—24 hours	24—48 hours	Total in 48 hours
176	10.30 '46	+51	227	9.6	94.4	3.8	98.2
	11.18 '46	+ 3	—	1.6	—	—	—
177	2.5 '47	+36	167	14.5	85.7	11.6	97.3
178	3.11 '48	+46	131	10.2	87.2	7.0	94.2
	4.7 '48	+64	—	4.6	—	—	—

All three patients presented a clinical picture of moderately severe thyrotoxicosis. There was, however, no enlargement of the thyroid gland. Two of the patients had had previous thyroidectomies. The results of the laboratory tests are presented in Table 19.

The basal metabolic rate and the serum protein-bound iodine were elevated, as is typically observed in endogenous thyrotoxicosis. The urinary excretion of I^{131} in all three patients was higher than normal. In fact it was almost 100 per cent. In endogenous thyrotoxicosis the I^{131}-excretion is characteristically lower than normal. When the thyroid medication was discontinued, the serum protein-bound iodine fell to a subnormal level in Case 176 and to a normal level in Case 178.

The very high excretion of I^{131} in these patients probably is due to a depression of the activity of the normal thyroid. Such a depression of thyroid function from thyroid medication has been observed previously (Farquharson and Squires, 1941; Riggs, Man, and Winkler, 1945). It is also possible that inorganic iodine is formed when the thyroid hormone is metabolized and that this iodine to some extent increases the excretion of I^{131}. However, the excretion of I^{131} is low in endogenous thyrotoxicosis when just as much thyroid hormone is metabolized. A possible objection to the interpretation of the mechanism for the high excretion of I^{131} is that two of these patients had previous thyroidectomies and therefore had little or no thyroid tissue left to collect I^{131}. However, Case 178 was shown to have a thyroid that was capable of manufacturing thyroid hormone at a normal rate. Furthermore, the same pattern of elevated serum protein-bound iodine and increased excretion of I^{131} (although still within normal limits) was observed in another patient (Case 335) who had been taking fairly large doses of thyroid for five years. Following cessation of thyroid, the serum protein-bound iodine fell to normal and the excretion of I^{131} decreased (see Table 28, p. 91).

The diagnostic significance of the peculiar combination of high BMR, high PBI, and high excretion of I^{131} will be discussed in Chapter IX.

Euthyroidism

Patients with thyroid disease who are in a euthyroid state generally have a goiter, and for the purpose of this discussion such patients are divided into three groups: nontoxic goiter, carcinoma, and chronic thyroiditis.

No confusion is likely about the terms "carcinoma" and "chronic thyroiditis," but "nontoxic goiter" is used in a more limited way than the expression implies. Actually all that it means is that it is a goiter not associated with hyperfunction of the thyroid. A more specific term, in order to rule out hypothyroid goiters, would be euthyroid goiter. However, the term nontoxic goiter is so widely employed that it will be used here to mean euthyroid goiter apart from malignancies and chronic thyroiditis.

The following classification was considered suitable:

1. Nontoxic goiter caused by excessive colloid storage, engorgement, benign neoplasms, and cystic degeneration.
   a) Patients in whom the clinical diagnosis of euthyroidism was apparent at the time of study.
   b) Patients in whom the diagnosis of euthyroidism was not established at the time of study.
2. Carcinoma of the thyroid.
3. Chronic thyroiditis.

The subdivision of the first group was made entirely for practical reasons. The patients belonging to group 1 b will also be discussed in Chapter IX on the differential diagnosis of thyrotoxicosis.

The objective was to study laboratory methods, particularly the radioactive iodine tolerance test in patients with euthyroid goiters. The results of such studies should not differ from those obtained in euthyroid patients without goiter or in normal subjects, if the radioactive iodine tolerance test accurately pictures the functional state of the thyroid.

1. Nontoxic goiter

a) *Patients in whom the clinical diagnosis of euthyroidism was apparent at the time of study.*

This group consisted of 41 patients (Cases 188—228), in whom there was no doubt about the clinical diagnosis of nontoxic goiter. Thirty-eight patients were women and three were men. The ages varied between 23 and 75 years. The chief complaint in most of the patients was swelling of the neck. Symptoms and signs suggestive of hyper- or hypothyroidism were exceedingly rare. The size of the thyroid, as judged by palpation, varied between $1\,^1/_2$ and 8 times normal size. The pathological diagnoses of the resected goiters are presented in Table 20. A variety of

Table 20. **The pathological diagnosis of thyroid tissue removed from patients with clinically apparent nontoxic goiter.**

	Number of patients
Struma nodosa tubularis (fetal adenoma)	6
Struma nodosa micro et macro follicularis (simple adenoma)	14
Struma nodosa macro follicularis (colloid adenoma)	12
Struma diffusa macrofollicularis (colloid goiter)	4
Hyperplastic adenoma	1
Multiple cysts	1
Amyloidosis	1
No operation	2[1]

[1] 1 probably Struma nodosa micro et macro follicularis.
1 probably Struma diffusa macro follicularis.

pathological conditions were represented. Marked hyperplasia was found in only one patient who had a BMR of —21 per cent. In two other patients small areas of slight hyperplasia were observed together with involution and hyperinvolution. None of these patients exhibited any symptoms or signs of thyrotoxicosis.

The basal metabolic rates obtained in 37 patients are presented in Fig. 12. In four patients no BMR was obtained. The average was —5 per cent. With the exception of the case with a BMR of —21 per cent, the values were within $\pm 3\,\sigma$ of

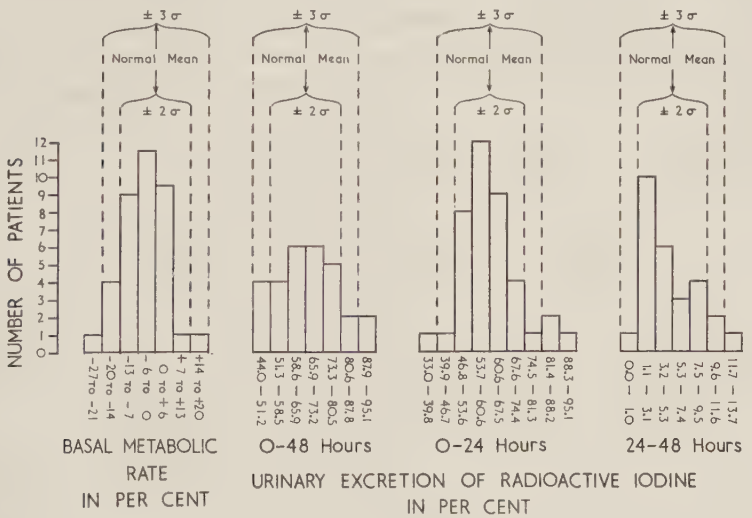

Fig. 12. The basal metabolic rate and the urinary excretion of I^{131} in patients with clinically apparent nontoxic goiter.

the normal mean (± 20 per cent). In 31 patients the BMR's were within $\pm 2\,\sigma$ of the normal mean.

The serum cholesterol, determined in 12 patients, was normal in 11 cases and elevated in one patient. The serum protein-bound iodine was determined in too few patients to permit an analysis of the results.

The results of the radioactive iodine tolerance test are presented in Fig. 12. Complete urine collections for 48 hours were obtained in 29 cases. The failure to obtain urine specimens for 48 hours in all patients was due primarily to surgical operations performed before the test was completed. However, in all but two patients, excretion data for the first 24 hours were obtained. These figures will be satisfactory for the comparison of this group with normal individuals.

The 48-hour urinary excretion of I^{131} varied between 45.5 per cent and 90.6 per cent with an average of 66.6 ± 2.2 per cent. This value does not differ from the normal average of 65.9 ± 0.7 per cent. Still more important is the fact that only two values were more than $\pm 3\,\sigma$ from the normal mean. Both values were slightly higher than normal (89.8 and 90.6 per cent, respectively). *In no case did the radioactive iodine tolerance test suggest hyperthyroidism.*

The 24-hour excretion, determined in 39 cases, varied between 37.4 and 88.5 per cent with an average of $59.9 \pm 1{,}7$ per cent. This mean value agrees well with the normal average of 60.6 ± 0.7 per cent. As for the variation, three values were above and one value below the $3\,\sigma$ limit.

The 24—48 hour excretion, determined in 27 cases, was within the normal $3\,\sigma$ limit with the exception of one patient whose excretion was slightly elevated. This patient, Case 210, had amyloidosis of the thyroid. It is possible that amyloid disease of the kidneys was responsible for the high excretion on the second day (compare the results of the radioactive iodine tolerance test in renal disease, Table 30, p. 96).

It will be demonstrated that in myxedema the excretion of I^{131} is characteristically higher than normal during the second day of the test. Since in this group of patients with nontoxic goiter there were a number of patients with a BMR in the low normal range, it is of interest to note that the excretion of I^{131} during the 24—48 hour period was normal, with the exception of the one case referred to above.

As stated previously, there was a great deal of variation in the pathology of the thyroids. There was no apparent relation between the excretion of I^{131} and the structural changes of the thyroid. Iodine deficiency may be an etiological factor in colloid goiter. Such goiters could therefore be expected to have an increased avidity for iodine, and consequently a low urinary excretion of radioactive iodine. In the present group there were 16 patients who could be classified as having colloid goiter, either as colloid adenoma or as diffuse colloid goiter. Furthermore, in several of the patients with simple adenoma the macrofollicular type was predominant. In all of these patients the radioactive iodine excretion was never below normal. *These results demonstrate that the presence of colloid goiter does not limit the usefulness of the radioactive iodine tolerance test in evaluating thyroid function.*

There is no indication that the size of the thyroid influences the radioactive iodine tolerance test. Despite the fact that nine patients had goiters weighing more than 50 grams and three weighing more than 100 grams, the urinary excretion of I^{131} was normal.

By giving normal values in patients with nontoxic goiter, the radioactive iodine tolerance test fulfills an important requirement of a test to be used for the evaluation of the functional state of the thyroid.

In summary, radioactive iodine tolerance tests were carried out in 41 patients with clinically apparent nontoxic goiters. The 48-hour urinary excretion of I^{131}, determined in 29 patients, was normal in 27 patients and slightly higher than normal in two patients. In no case did the test indicate hyperthyroidism. The 24-hour excretion, determined in 39 patients, was normal in 35 cases, slightly below normal in one case, and somewhat above normal in three cases. Thus, in one patient the value for the 24-hour excretion did suggest an increased avidity for iodine. On the whole, however, the radioactive iodine tolerance test gave a clear picture of the functional state of the thyroid in this group. There is no indication that the presence of colloid goiter will disturb the test.

b) *Patients in whom the diagnosis of euthyroidism was not established at the time of study.*

The group consisted of 39 patients with 33 women and six men (Cases 229—267). The ages varied between 17 and 75 years. The group is heterogeneous, but the feature common to all patients was the suspicion of thyrotoxicosis at the time of study due to the presence of goiter in addition to other suggestive findings. A detailed discussion of the symptomatology and the diagnostic problems in all these patients is given in Chapter IX. The final diagnosis in most patients was that of nontoxic goiter with some unrelated disorder. Table 11 (p. 49) indicates the unrelated diseases with which the present group of nontoxic goiters was associated.

From the practical point of view these patients were studied to determine whether or not they had thyrotoxicosis. The later clinical course, further studies, the result of treatment, and the follow-up served to establish the diagnosis of nontoxic goiter with reasonable certainty. The diagnostic classification was made without any attention to the results of the laboratory tests. It should be admitted that in a number of these patients the probability of thyrotoxicosis was rather remote. An anatomic diagnosis of nontoxic goiter was obtained in the nine cases who had thyroidectomy.

The results of the determinations of basal metabolic rate, serum cholesterol, serum protein-bound iodine, and radioactive iodine excretion are presented graphically in Fig. 13 and Fig. 14.

The BMR varied between —16 and +49 per cent with an average of +12 per cent. In two patients a BMR was not obtained because of technical difficulties. In 10 patients (26 per cent) the BMR was definitely elevated. These results illustrate the

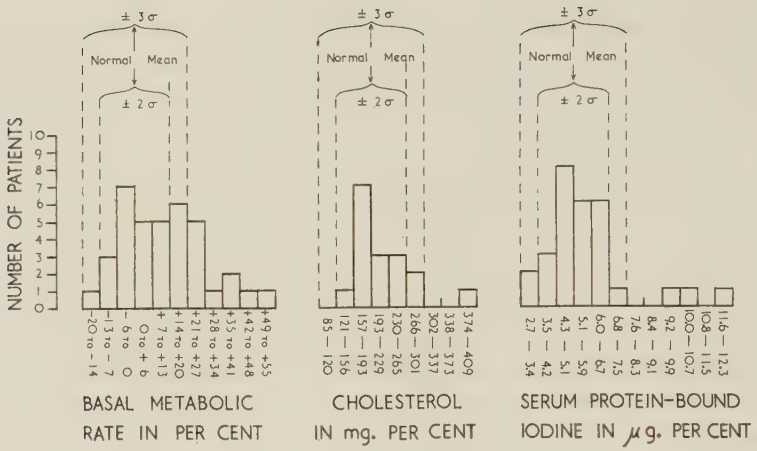

Fig. 13. The basal metabolic rate, the serum cholesterol, and the serum protein-bound iodine in patients with nontoxic goiter, in whom the diagnosis was not established at the time of study.

well-known fact that there are a number of extrathyroidal factors that may cause elevation of the basal metabolic rate. In the presence of such complications the BMR cannot be used to rule in or out thyrotoxicosis. The results also suggest that, even in the absence of such complications, the basal metabolic rate may not always give a true picture of the functional state of the thyroid.

The serum cholesterol, determined in 17 cases, was within the normal range in all but one patient, in whom it was elevated.

The serum protein-bound iodine was determined in 29 patients. It was within $\pm 3\,\sigma$ of the normal mean in 26 patients. In three patients it was elevated. In Case 267 the elevated PBI was almost certainly due to an analytical error, as two later determinations gave normal values in spite of no particular change of the clinical picture. In the two other patients (Cases 238 and 266) it must be admitted that the PBI gave a misleading picture of thyroid function. But in 90 per cent of the analyses the PBI was compatible with the final diagnosis. It is apparent that the serum protein-bound iodine was a better measure of thyroid function than was the basal metabolic rate.

The results of the radioactive iodine tolerance test are presented in Fig. 14. The 48-hour urinary excretion of I^{131} varied between 49.8 and 90.8 per cent with an average of 64.6 $\pm$ 1.6 per cent. This value does not differ significantly from the normal average of 65.9 $\pm$ 0.7 per cent. From the practical point of view it is most important that in none of the 39 patients was the excretion below the normal range. Two patients had an excretion slightly higher than normal. The 24-hour excretion, determined in 37 patients, varied between 43.2 and 82.3 per cent with an average of 59.6 $\pm$ 1.6 per cent. This average is in good agreement with the normal mean of 60.6 $\pm$ 0.7 per cent. The individual values fell within $\pm$ 3 σ of the normal mean except in one patient in whom the excretion was slightly higher than normal.

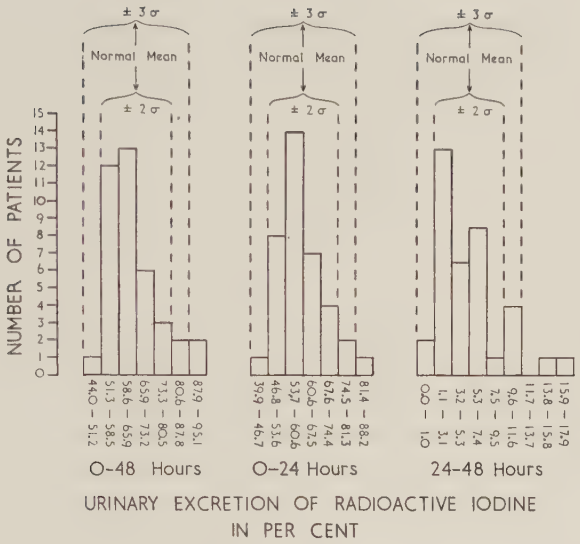

Fig. 14. The urinary excretion of I^{131} in patients with nontoxic goiter in whom the diagnosis was not established at the time of study.

The 24—48 hour excretion, determined in 37 patients, varied between 0.5 and 16.4 per cent with a mean of 5.2 ± 0.6 per cent, which is almost identical with the normal mean. In two patients, Cases 238 and 256, the excretion was higher than normal, a result consistent with values invariably observed in myxedema, and sometimes associated with renal impairment.

In no patient did the radioactive iodine tolerance test give results suggestive of thyrotoxicosis. This shows that the test is a good measure of thyroid function in patients with nontoxic goiter even when certain symptoms and signs suggest thyrotoxicosis, or when the nontoxic goiter is complicated by a variety of other diseases that obscure the clinical picture. It is apparent that the radioactive iodine tolerance test was a much more reliable measure of thyroid function than was the basal metabolic rate in this group of patients. In comparison with the serum protein-bound iodine the radioactive iodine tolerance test was at least as reliable and perhaps more so. The serum protein-bound iodine was elevated to thyrotoxic levels in three of 29 patients, while the radioactive iodine excretion indicated thyrotoxicosis in none of 39 patients. In two patients the excretion pattern of I^{131} was compatible with myxedema. This fact did not cause any diagnostic confusion.

2. Carcinoma of the thyroid

Carcinoma of the thyroid very rarely is accompanied by disturbances in the hormonal function of the thyroid. It is most uncommon for carcinoma of the thyroid to destroy so much of the gland that the patient becomes myxedematous. Hyper-

thyroidism caused by hyperfunctioning cancer of the thyroid is very rare also, but a few such cases have been reported. In some of these cases, however, the carcinoma was not satisfactorily demonstrated to be the cause of the hyperthyroidism. When carcinoma of the thyroid and hyperthyroidism are associated, there are usually histologic changes in the nonmalignant tissue to account for the hyperthyroidism. Pemberton and Black (1948), in a series of about 3500 cases of thyrotoxicosis, found thyroid carcinoma in 0.4 per cent. In none of these patients was the tumor considered to cause the thyrotoxicosis. Thus, hyperthyroidism produced by a thyroid carcinoma is very rare. Studies of the collection of radioactive iodine by carcinomatous thyroid tissue also support this thesis. Recently, however, Leiter, Seidlin, Marinelli, and Baumann (1946) reported a case in whom a thyroid carcinoma undoubtedly caused hyperthyroidism (see Table 4, p. 18).

Hamilton, Soley, and Eichorn (1940) using radioautographic technique, observed that almost no iodine was concentrated in cancerous thyroid tissue. With a similar technique Marinelli, Foote, Hill, and Hocker (1947) demonstrated that "benign metastazing struma" and certain follicular adenocarcinomas were able to pick up radioactive iodine. Rawson, McArthur, Dobyns, Fluharty, and Cope (1948) observed that some thyroid carcinomas as well as their metastases collected minimal amounts of radioactive iodine. In comparison with normal thyroid tissue the concentration of radioactive iodine was small.

This study of thyroid carcinoma was made primarily to determine if the presence of the tumor would in any respect interfere with the use of the radioactive iodine tolerance test for evaluating thyroid function.

Twenty-five patients with thyroid carcinoma (Cases 268—292) were studied.[1] Three patients (Cases 289, 290, and 291) are excluded from the present discussion because of thyroid medication at the time of or immediately before the study, and one patient (Case 292) because no studies were done prior to total thyroidectomy. The results of the laboratory tests are presented in Table 21. Most of the patients had papillary adenocarcinoma, but a number of other types of thyroid carcinoma were represented. As indicated in Table 21, several of the patients had subtotal thyroidectomy or were treated with X-rays prior to this study. At the time of study all patients were in a euthyroid state. This was rather obvious in the majority of the patients. None of them presented clinical hypothyroidism. Two patients, Cases 284 and 288, presented a clinical picture somewhat suggestive of thyrotoxicosis.

The basal metabolic rate, determined in 17 patients, was normal except in the two patients in whom thyrotoxicosis was suspected.

The serum cholesterol, determined in 10 patients, was normal in eight patients and definitely elevated in two patients. The elevated cholesterol values were probably due to approaching myxedema that was not yet recognized clinically.

The serum protein-bound iodine, determined in eight patients, was normal in all

[1] Two patients (Cases 293 and 294) were excluded as the diagnosis of thyroid carcinoma was not definitely proved. Both had normal excretion of I^{131}.

Table 21. The laboratory tests in p

Case number	Age Sex	Thyroid size and type[1]	Cholesterol mg per cent	BMR per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent			Pathological diagnosis	Remarks
						0—24 hours	24—48 hours	Total in 48 hours		
268	50 ♂	2, N, f		+ 6	6.4			57.3	Papillary adenocarcinoma	
269	25 ♀	1 ½, N, h	284	+ 1		64.0			» »	
270	61 ♀	1, D, f	212	— 3		64.7	8.0	72.7	» »	Subtotal thyroidectomy 7 months prior to study
271	56 ♀	1 ½, N, h		—10		57.5	6.0	63.5	» »	
272	36 ♂	1 ½, N, f		—16	4.6	78.3	0.0	78.3	» »	
273	49 ♀	1, D, f				69.8	4.9	74.7	» »	Subtotal thyroidectomy 2 months prior to study
274	66 ♂	1, N, f		— 1		60.3	10.8	71.1	» »	
275	26 ♂	2, D, h	205	—20		69.9	4.4	74.3	» »	
276	30 ♀	1, N, f		+16		52.7	2.9	55.6	» »	
277	60 ♀	2, N, h	384		2.4	84.0	5.6	89.6	» »	X-ray treatment to the neck (6000 r) 2 months prior to study
278	29 ♀	<1, N, f	357	—16		49.8	1.0	50.8	» »	Subtotal thyroidectomy 2 ½ months prior to study
279	74 ♀	4, N, h	275	+ 2				65.0*	» »	* Calculated from in vivo measurements
280	59 ♂	1 ½, N, f		— 2		45.5	8.1	53.6	» »	
281	60 ♂	1 ½, N, f						66.4	Alveolar adenocarcinoma	
282	37 ♀	1 ½, N, h		+ 7		57.4	1.6	59.0	» »	
283	51 ♀	1 ½, N, h	227	+ 5	4.4	52.5	5.2	57.9	» »	
284	58 ♀	2 ½, N, f	170	+23	5.5	45.5	8.1	53.6	» »	
285	50 ♂	1 ½, N, f		— 4		67.7	3.0	70.7	Small-cell carcinoma	Subtotal thyroidectomy 3 ½ months prior to study
286	57 ♂	not definitely palpable		—14	4.0	82.5	8.5	91.0	» »	Subtotal thyroidectomy 3 months prior to study
287	46 ♀	1, D, f	194		3.7	59.1	7.8	66.9	Giant-cell carcinoma	Subtotal thyroidectomy 5 months prior to study
288	32 ♀	2 ½, N, f	98	+41	4.8	69.4	3.6	73.0	»Spindle-cell» carcinoma	X-ray treatment (9000 r) to the neck 3 months prior to study

[1] Numbers indicate thyroid size as compared to normal; D=diffuse, N=nodular, f=firm, h=hard.

but one case. It was below normal in Case 277, who had received 6000 roentgens to her neck two months prior to the study. There was, however, no clinical myxedema.

The 48-hour urinary excretion of I^{131}, determined in 20 patients, varied between 50.8 per cent and 91.0 per cent with an average of 67.3 $\pm$ 2.5 per cent. This average does not differ significantly from the normal. In 18 patients the individual values were within the normal $\pm 3\sigma$ limit, while in Cases 277 and 286 the excretion was slightly higher than normal. However, the excretion pattern was normal even in these patients. The 24-hour excretion, determined in 18 patients, varied between 45.5 and 84.0 per cent with an average of 62.8 $\pm$ 2.7 per cent, thus agreeing well with the normal mean. The distribution of the individual values was similar to those for 48 hours. Cases 277 and 286 had increased excretion for 24 hours. The 24—48 hour excretion, determined in 17 patients, was invariably in the normal range.

The present results agree well with those reported by Keating *et al.* (1947) in 10 patients with papillary adenocarcinoma of the thyroid (Table 4, p. 18).

The results of the radioactive iodine tolerance test in patients with carcinoma of the thyroid show that thyroid carcinoma *per se* does not interfere with the test.

In no patient did the radioactive iodine tolerance test suggest thyrotoxicosis. This result was of diagnostic value in Cases 284 and 288, who are discussed more fully in Chapter IX.

Unfortunately, there was no opportunity to study patients with thyrotoxicosis caused by hyperfunctioning carcinoma. It may be predicted that the radioactive iodine tolerance test under such circumstances would give results as in ordinary thyrotoxicosis.

Despite relatively low basal metabolic rates in several patients, the radioactive iodine tolerance test did not suggest myxedema. This result was in agreement with the clinical findings.

A tentative diagnosis of thyroid malignancy often can be made from the clinical findings. However, in many patients the diagnosis can not be established without histological examination. The urinary excretion of radioactive iodine does not assist in the diagnosis of thyroid malignancy. With special arrangements for *in situ* measurements for the localization of the radioactive iodine in thyroid nodules, the diagnosis of thyroid malignancy can be made more accurately (Dobyns, Skanse, and Maloof, 1949).

In conclusion, the radioactive iodine tolerance test generally gives normal values in euthyroid patients with carcinoma of the thyroid. There is no indication that the presence of thyroid carcinoma diminishes the usefulness of the radioactive iodine tolerance test in evaluating thyroid function. The urinary excretion of I^{131} is of no assistance in the diagnosis of thyroid malignancy *per se*. The test can be used to exclude thyrotoxicosis in patients with thyroid carcinoma. It may be anticipated that the test will give a true picture of thyroid function even in the rare instances when a thyroid carcinoma causes hyperthyroidism or hypothyroidism.

3. Chronic thyroiditis

Chronic thyroiditis is chiefly of two types, the Hashimoto type and the Riedel type. The thyroid function may or may not be disturbed in patients with chronic thyroiditis. The pathologic process is apt to progress slowly, but it will gradually destroy the normal thyroid structure. Sooner or later during the course of the disease thyroid deficiency is likely to occur. Usually the hypofunction does not appear until late in the disease.

Hyperthyroidism from chronic thyroiditis has been reported by Brünger (1914), Reist (1922), and others, while Lee (1936) and Means (1948), for example, doubt its existence. It is conceivable, that a transient hyperthyroidism might occur in the early stages of the disease.

The objective of the present study was to determine whether the radioactive iodine tolerance test could be used to evaluate thyroid function in patients with chronic thyroiditis. It was necessary to know whether the mere presence of chronic thyroiditis would disturb the test.

Eleven patients with chronic thyroiditis and euthyroidism were studied (Cases 295—305). In Case 298 there was some suggestion of thyroid hypofunction, but a clinical diagnosis of myxedema could not be made. Two patients (Cases 306 and 307), who also had clinical myxedema, will be discussed together with other patients with hypothyroidism, but the results of the radioactive iodine tolerance tests will be used for comparison.

The chronic thyroiditis was of the Hashimoto type in nine patients and of the Riedel type in two patients (pathological diagnosis). The results of the laboratory tests are presented in Table 22.

The basal metabolic rate, determined in 10 patients, varied considerably. Two patients had BMR's above and two patients below the normal $\pm 3\,\sigma$ limit. The serum cholesterol, determined in six patients, was normal.

The serum protein-bound iodine, determined in only four patients, was normal in three patients and below normal in one patient (Case 303). This low value was not compatible with the clinical findings.

The radioactive iodine tolerance test exhibited a good deal of variation. The 48-hour excretion was within $\pm 3\,\sigma$ of the normal mean in nine patients and higher than normal in two patients. Corresponding results were obtained for the 24-hour excretion. The 24—48 hour excretion was more than $3\,\sigma$ above the normal mean in three patients. It will be demonstrated that the 24—48 hour excretion of I^{131} is constantly elevated in myxedema. This tendency of clinically euthyroid patients with chronic thyroiditis to give high excretion values during the second day of the test may be a sign of developing myxedema. However, an elevated second-day excretion was found in one patient with a BMR of + 26 per cent. In the two other patients the BMR's were —15 per cent and —26 per cent, respectively. It may be

Table 22. **The laboratory tests in patients with chronic thyroiditis.**

Case number	Age Sex	Thyroid size and type[1]	Cholesterol mg per cent	BMR per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent			Pathological type
						0—24 hours	24—48 hours	Total in 48 hours	
295	69 ♂	2, D, f		+26	4.7	69.3	14.8	84.1	Hashimoto
296	52 ♀	2, N, f	269	— 1		79.7	4.7	84.4	»
297	62 ♀	3, N, f		— 3		57.1	2.3	59.4	»
298	66 ♀	2 ½, N, f	301	—26		53.7	12.6	66.3	»
299	24 ♀	1 ½, N, f				70.0	8.4	78.4	»
300	16 ♀	2, D, s	223	— 5	5.9	59.2	1.3	60.5	»
301	33 ♀	2—3, D, f		—22		82.3	8.4	90.7	»
302	10 ♀	2, N, f	189	—15		44.7	11.8	56.5	»
303	42 ♀	2, D, f	236	+ 5	2.4	51.3	6.0	57.3	»
304	57 ♀	1 ½, D, h		+12		84.5	10.2	94.7	Riedel
305	62 ♀	3, N, h	160	+21	4.0	55.8	7.4	63.2	»

[1] Numbers indicate thyroid size as compared to normal; D=diffuse, N=nodular, s=soft, f=firm, h=hard.

mentioned in advance that the two patients with chronic thyroiditis and myxedema had elevated excretion values for the 24—48 hour period.

The possibility of thyrotoxicosis was raised in Cases 295 and 305 primarily because of goiter associated with elevated basal metabolic rate. The radioactive iodine tolerance test was of value in ruling out thyrotoxicosis. These two patients will be fully discussed in Chapter IX on the differential diagnosis of thyrotoxicosis.

Because of low BMR's myxedema was suspected in Cases 298 and 301, but a definite diagnosis of myxedema was not established preoperatively. The radioactive iodine tolerance test was not typical of myxedema, although the second-day excretion in Case 298 was higher than normal.

The diagnosis of chronic thyroiditis sometimes can be made clinically. Very often, however, the diagnosis cannot be established without microscopic examination of the gland. The radioactive iodine tolerance test does not in itself contribute to the diagnosis of chronic thyroiditis. The results demonstrate, however, that the radioactive iodine tolerance test is useful in estimating the functional state of the thyroid even in chronic thyroiditis.

In summary, the urinary excretion of I^{131} is normal in most of clinically euthyroid patients with chronic thyroiditis. In certain patients the excretion is higher than normal, or it approaches the pattern observed in myxedema. This should probably be interpreted as a sign of developing myxedema.

Hypothyroidism

1. Myxedema

Hypothyroidism by definition means a decreased production of thyroid hormone. Such a hypofunction of the thyroid leads to the well-defined clinical entity of myxedema. There are several varieties of myxedema. The primary disturbance may be either in the thyroid or in the anterior pituitary. However, a discussion of the pathogenesis of myxedema is not within the scope of the present investigation.

It is obvious that the decreased formation of the iodine-containing thyroid hormone will disturb the metabolism of iodine. The objective of the present study primarily was to determine whether the urinary excretion of I^{131} in myxedematous patients differed in any characteristic way from that of normal individuals. One might expect to find such a difference. For the diagnostic use of the radioactive iodine tolerance test in myxedema it is also necessary to know whether such a deviation from the normal is specific for myxedema.

The diagnosis of myxedema was made from the history, the clinical findings, and the basal metabolic rate. The response to specific treatment with thyroid gave further support for the diagnosis in case of uncertainty. In most of the patients reported in this group there were no diagnostic difficulties.

Twenty-six patients were studied (Cases 278, 279, and 306—329). Twenty-three were females and three were males. The ages varied between 25 and 77 years with the exception of a one-year-old cretin infant. Eighteen patients were more than 50 years old. The cause of the myxedema varied as seen in Table 23. Two patients had pituitary myxedema. Chronic thyroiditis caused the hypothyroidism in two other patients. In most cases the thyroid gland was not palpable, but a goiter was present in the two patients with chronic thyroiditis and in one patient in whom the etiology was unknown.

The clinical picture in most patients was that of classic myxedema. In six cases the clinical picture was somewhat obscured by complicating diseases: cardiovascular disease (4 cases), multiple sclerosis (1 case), and diabetes mellitus (1 case).

Table 23. **The etiology of myxedema observed in the present study.**

	Number of patients
Primary atrophy	15
Cretinism	1
Postoperative	5[1]
Chronic thyroiditis	2
Pituitary myxedema	2
? Goitrogen of unknown origin	1

[1] In three patients following total thyroidectomy for carcinoma of the thyroid.

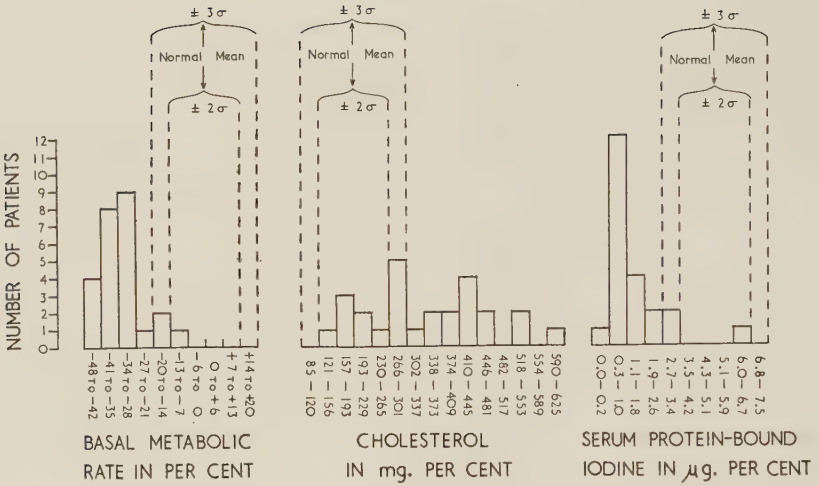

Fig. 15. The basal metabolic rate, the serum cholesterol, and the serum protein-bound iodine in patients with myxedema.

The laboratory data are presented in Fig. 15 and Fig. 16.

The basal metabolic rate was below the normal $-3\,\sigma$ limit in 22 patients, below the normal $-2\,\sigma$ limit in 24 patients, and within the normal $\pm 2\,\sigma$ limit in one patient. This last patient, however, showed a subnormal BMR when examined one month later. The BMR was not determined in the cretin infant. As expected, the BMR generally was decreased. It is possible that clinical myxedema may exist with a BMR within the normal range. This can probably occur in patients who run a comparatively high BMR when healthy. Usually, however, the fall in basal metabolic rate precedes the appearance of clinical myxedema, as can be observed in patients after complete surgical removal of the thyroid. This phenomenon may also be observed in patients with chronic thyroiditis where the thyroid gland is gradually destroyed (compare Table 22, p. 78).

The serum cholesterol was higher than the normal $+3\,\sigma$ limit in 14 patients and higher than the normal $+2\,\sigma$ limit in 19 patients, but was normal in seven patients. Thus, the serum cholesterol is normal in a rather high percentage of patients with myxedema. Elevated cholesterol values are also found in a variety of other diseases as, for example, nephrosis, diabetes mellitus, and biliary obstruction. When such other diseases can be excluded, an elevated serum cholesterol favors the diagnosis of myxedema, but a normal value cannot be used to exclude myxedema. The results generally agree with those previously reported in the literature (Epstein and Lande, 1922; Hurxthal, 1934; and others).

The serum protein-bound iodine was determined in 22 patients. It was below the normal $-3\,\sigma$ limit in 19 patients and below the normal $-2\,\sigma$ limit in 21 patients and was normal in one patient. This last patient had a value (6.2 μg. per cent) that

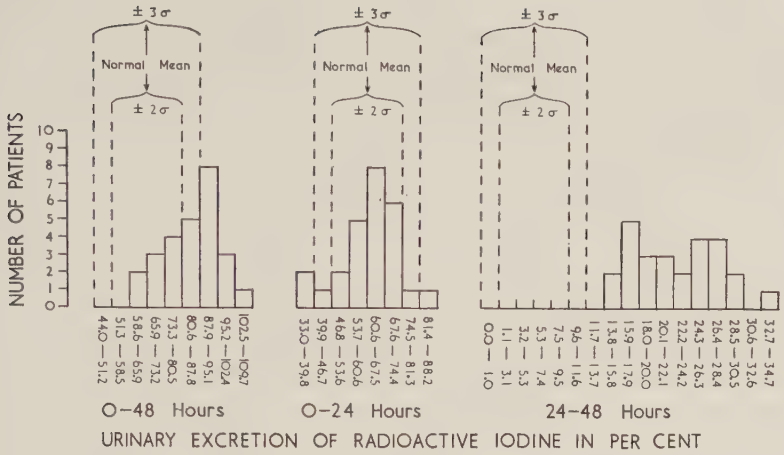

Fig. 16. The urinary excretion of I^{131} in patients with myxedema.

was not at all in keeping with the other results. The explanation of this failure was not found. The results suggest that the serum protein-bound iodine is of value in establishing the diagnosis of myxedema. It is possible that a low serum protein-bound iodine is an indication for treatment with thyroid even when there is no definite clinical myxedema. The results of the determinations of serum protein-bound iodine in myxedema agree rather well with those reported by Salter, Bassett, and Sappington (1941), Winkler, Riggs, and Man (1945), Riggs (1947), and Winkler (1947) (See Table 2 p. 12).

The results of the radioactive iodine tolerance test are presented graphically in Fig. 16. Complete urine collections for 48 hours were obtained in all 26 patients. The average 48-hour urinary excretion was 83.6 $\pm$ 2.1 per cent. This value is significantly higher than the normal average of 65.9 $\pm$ 0.7 per cent. There was, however, a considerable overlapping with the normals. No less than 14 patients gave values below $+3\,\sigma$ of the normal mean and nine below $+2\,\sigma$ of the normal mean. Thus it is apparent that the total 48-hour excretion of radioactive iodine is an unreliable test for demonstrating hypofunction of the thyroid in an individual case. When a higher than normal excretion appears, this is suggestive of hypothyroidism, provided that other causes for abnormally high excretion of I^{131} can be excluded.

Greater deviations from normal were found when the values for the first and the second 24-hour periods were analyzed separately. The 0—24 hour excretion averaged 61.4 $\pm$ 2.3 per cent which does not differ significantly from the normal average. The 24—48 hour excretion varied between 15.2 and 34.6 per cent with a mean of 22.6 $\pm$ 1.0 per cent. Thus, in myxedema the second-day excretion is much higher than the average of 5.3 $\pm$ 0.2 per cent observed in the normals. Most important from the point of view of using this test for diagnostic purposes was the fact that all values in patients with myxedema definitely fell above the normal

$+3\,\sigma$ limit. *Thus, the high second-day excretion is characteristic of myxedema.* It is not absolutely specific, however, as similar values may be observed in certain patients with cardiovascular and renal disease.

This pattern of excretion of radioactive iodine in myxedema was observed earlier by HAMILTON and SOLEY (1939), KEATING *et al.* (1947), and SKANSE (1948 b). The number of patients in these earlier reports was too small, however, to permit a statistical analysis. There are several possible explanations for the delayed excretion of I^{131} in patients with myxedema. The ability of the kidneys to excrete iodine may be impaired due to the lack of thyroid hormone. This thesis is supported by the finding of abnormally low renal blood flow and glomerular filtration in two patients with myxedema in whom treatment with thyroid resulted in improved renal clearances (CORCORAN and PAGE, 1947). There may be a retarded resorption of the iodide from the gastro-intestinal tract. A greater than normal amount of I^{131} may go into the peripheral tissues for some period of time before it is excreted by the kidneys. The present studies do not permit any conclusions concerning the mechanism that is responsible for the abnormal pattern of radioactive iodine excretion in myxedema.

In conclusion, the urinary excretion of I^{131} in 26 cases of myxedema was characterized by an excretion, invariably higher than normal, during the 24—48 hour period. The total 48-hour excretion was normal or elevated. The consistent pattern of the radioactive iodine excretion suggests that this test might be used in the diagnosis of myxedema. For this purpose, however, it is necessary also to study the behavior of the test in diseases that simulate myxedema.

2. Hypothyroidism due to thiocyanate

Potassium thiocyanate has been used extensively in the treatment of hypertension. BARKER (1936) and others observed that goiters associated with low basal metabolic rates developed in a few hypertensive patients treated with thiocyanate for long periods of time. Later studies revealed that thiocyanate acted as a goitrogen by inhibiting the thyroid's collection of the iodide ion (FRANKLIN, CHAIKOFF, and LERNER, 1944; VANDERLAAN and BISSELL, 1946).

In the present investigation two patients were observed with hypothyroidism due to thiocyanate therapy. Case 330 had a goiter that disappeared following discontinuation of thiocyanate administration, while in Case 331 there was no apparent goiter. The results of the different laboratory tests are presented in Table 24.

The results may appear confusing at first. The combination of low BMR, low PBI, and normal or low excretion of I^{131} has not appeared in patients previously discussed. However, the results may be readily explained. The thiocyanate medication prevented a normal collection of iodine in the thyroid, the production of thyroid hormone decreased, and the thyroid gland became hyperplastic, probably through an increased

Table 24. **The effect of thiocyanate on thyroid function.**

Case number	Date	BMR per cent	Cholesterol mg per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent			Serum KSCN mg per cent	Remarks
					0—24 hours	24—48 hours	Total in 48 hours		
330	10.15 '47	—38	298	1.7	37.8	12.2	50.0	—	KSCN 1945
	10.29 '47	— 7	197	3.4 (11.7)	28.3	2.1	30.4	5.5	—10.14 '47
	3.12 '48	—24	287	4.9	47.6	9.2	56.8	—	
331	9.19 '47	—11	—	—	—	—	—	—	KSCN
	11.5 '47	—13	—	0.6	—	—	—	—	started
	11.20 '47	— 9	—	3.3	—	—	33.4	4.9	8.12 '47, dis-
	12.8 '47	—	—	4.5	44.5	2.6	47.1	1.8	continued before 11.5 '47
332	1.20 '48	—22	—	—	46.4	12.2	58.6	9.0 (11.20 '47)	KSCN since Nov. 1946
333	2.19 '48	—	—	3.3	70.4	5.1	75.5	13.8	KSCN since July 1947

action of thyrotropic hormone. Thus, the thyroid's real avidity for iodine increased, but it was blocked by the thiocyanate. When in Case 330 the first dose of I^{131} was given the day after cessation of the thiocyanate therapy, the excretion of I^{131} was in the low normal range despite the fact that the blood level of thiocyanate at that time must have been rather high. The thyroid then went through a phase of increased avidity for iodine (I^{131}-excretion: 30.4 per cent) before it adjusted itself to normal (I^{131}-excretion: 56.8 per cent). At that time the goiter as well as the symptoms of hypothyroidism had abated. The serum protein-bound iodine rose gradually from the hypothyroid to the euthyroid range. It should be observed that the collection of radioactive iodine by the thyroid decreased despite the increased output of thyroid hormone. The reason for the low BMR on the last examination is not clear. In Case 331 the course of events was similar, as were the laboratory tests.

For comparison two patients are included who were on thiocyanate therapy but who had not developed hypothyroidism. In both cases the 48-hour excretion of I^{131} was within normal limits. However, the abnormally high 24—48 hour excretion and the low BMR in Case 332 may indicate approaching hypothyroidism. In Case 333 the comparatively low serum protein-bound iodine may be interpreted in a similar fashion.

The combination of hypothyroidism and high collection of radioactive iodine was previously observed by Hamilton *et al.* (1943) in two patients in whom the etiology

Table 25. **The urinary excretion of radioactive iodine in patients with thyroid disease.**

Number of patients	Type of patients	Urinary excretion of I^{131} in per cent								
		0—24 hours			24—48 hours			Total in 48 hours		
		No.	$M \pm \varepsilon (M)$	σ	No.	$M \pm \varepsilon (M)$	σ	No.	$M \pm \varepsilon (M)$	σ
110	Normal subjects	110	60.6±0.7	6.9	110	5.3±0.2	2.1	110	65.9±0.7	7.3
94	Thyrotoxicosis without diagnostic problems	94	15.5±0.8	8.2	94	1.9±0.1	1.3	94	17.4±0.9	8.4
81	Thyrotoxicosis with diagnostic problems	77	26.6±1.2	10.9	75	2.2±0.2	2.0	75	29.0±1.3	11.5
3	Thyrotoxicosis factitia	3	89.1		3	7.5		3	96.6	
41	Nontoxic goiter without diagnostic problems	39	59.9±1.7	10.7	27	4.9±0.6	3.0	29	66.6±2.2	11.9
39	Nontoxic goiter with diagnostic problems	37	59.6±1.6	9.7	37	5.2±0.6	3.7	39	64.6±1.6	10.3
25	Carcinoma of the thyroid with euthyroidism	18	62.8±2.7	11.6	17	5.3±0.7	3.0	20	67.3±2.5	11.3
11	Chronic thyroiditis with euthyroidism	11	64.3±(4.1)	(13.6)	11	8.0±(1.3)	(4.2)	11	72.3±(4.3)	(14.4)
26	Myxedema	26	61.4±2.3	11.7	26	22.6±1.0	5.3	26	83.6±2.1	10.9

of the goiter was not established, and by Rawson, Hertz, and Means (1943) in one case of thiocyanate goiter.

The combination of low BMR, low PBI, and low excretion of I^{131} is characteristic of the depression of thyroid function due to an antithyroid drug after the drug is omitted.

Summary of the Results of the Radioactive Iodine Tolerance Test in Thyroid Disease

The results of the radioactive iodine tolerance test in each group of patients with thyroid diseases have been dealt with separately. A comparison of the results in the different groups of patients can be made from Table 25, which summarizes the findings.

It is apparent that the urinary excretion of I^{131} in thyrotoxicosis is considerably less than in normal subjects. The excretion is decreased both for the 0—24 hour period and for the 24—48 hour period. The decreased excretion of I^{131} is due to the thyroid's increased avidity for iodine in thyrotoxicosis. These findings should be contrasted with the increased excretion of I^{131} observed in three patients in whom the thyrotoxic state was produced by excessive intake of thyroid.

In patients with different thyroid diseases associated with euthyroidism the urinary excretion of I^{131} is normal both for the 0—24 hour period and for the 24—48 hour period. These results show that the urinary excretion of I^{131} is not primarily influenced by structural changes in the thyroid. It is the functional state of the thyroid that affects the urinary excretion of I^{131}.

In myxedema the total 48-hour excretion of I^{131} is higher than normal. This increase is due to the strikingly elevated excretion during the 24—48 hour interval, while the 0—24 hour excretion is normal.

The results show that the urinary excretion of I^{131} is characteristically different in patients with various states of thyroid function. Thus, the radioactive iodine tolerance test can be used as a measure of thyroid function.

Chapter VII

FACTORS THAT MAY INFLUENCE THE RADIOACTIVE IODINE TOLERANCE TEST

The radioactive iodine tolerance test generally gives a clear picture of the functional state of the thyroid. There are, however, a number of extrathyroidal factors that may affect the test. These factors usually play the same rôle whether the urinary excretion or the collection of I^{131} by the thyroid is measured.

In general, all factors that might disturb the normal metabolism of iodine must be considered. The most important of these factors are the variations of iodine intake, the administration of iodine-containing drugs for therapeutic or diagnostic procedures (cholecystograms, etc.), the administration of antithyroid drugs, the resorption from the gastro-intestinal tract, and the state of kidney and heart function. The radiation from the I^{131} should also be considered. It is necessary to know the effect of these factors for the interpretation of the results obtained in the diagnostic use of the test. It may be mentioned in advance that none of these factors appreciably detracts from the clinical value of the radioactive iodine tolerance test.

Variations in Iodine Intake

The radioactive iodine administered for the tolerance test not only labels the inert carrier iodide but, as soon as it has entered the blood stream, it also labels all the iodide already present in the blood as well as the tissue iodide in osmotic equilibrium with the blood. Thus, the percentage collection or excretion of I^{131} will depend upon the amount of iodide that is actually labelled (compare p. 34). Assume, for instance, that in one case the I^{131} labels a total of 200 μg. of iodide and in another case a total of 2 000 μg. of iodide. If 100 μg. of iodide are collected by the thyroid it will mean that 50 per cent of the I^{131} is taken up in the first case, but only 5 per cent in the second case. Or, in other words, a collection of a certain percentage of I^{131} will mean very different avidity for iodine by the thyroid with a high or a low plasma iodide concentration.

Hertz, Roberts, Means, and Evans (1940) showed in rabbits that the thyroidal collection of radioactive iodine decreased when the quantity of inactive iodine administered was increased.

Normal variations in iodine intake

The inorganic serum iodide is of the magnitude of 1—2 μg. per cent (Salter, 1940). The serum iodide concentration obviously will vary with the intake of iodine in the food and water. There is a good deal of geographical variation in the iodine content of food and water. In Boston, where sea food is a regular part of the diet, the iodine intake is probably comparatively high. It is of interest to compare the present writer's results with those obtained in an inland district where the iodine intake is likely to be low. The urinary excretion of radioactive iodine in euthyroid individuals as reported from the Mayo Clinic, Minnesota, (Keating *et al.*, 1947) shows a surprisingly good agreement with the present data. This indicates that variations in the iodine content of food and water are not likely to be of any great practical importance.

Werner *et al.* (1948) claimed that the thyroid uptake of I^{131} is largely inhibited by previous administration of iodized table salt. However, data from a number of patients in the present study indicated that the use of iodized table salt did not interfere with the results of the radioactive iodine tolerance test.

It may be concluded that normal variations in the iodine intake do not significantly influence the radioactive iodine tolerance test.

Iodide medication

Iodide medication modifies the radioactive iodine tolerance test in two respects:

1. by producing a high level of plasma iodide, and
2. by producing a pharmacologic effect on the thyroid.

Iodine medication decreases the hyperactivity and hypersecretion of the gland. This effect is not accompanied by simultaneous changes in the clinical picture. Indeed, the decrease in hypersecretion of thyroid hormone precedes the clinical improvement. When iodine medication is stopped, the plasma iodide returns to normal in 2—3 days. It takes usually longer, however, before the thyroid gland recovers the avidity for iodine it had prior to the iodine medication. The length of this interval probably varies considerably among different individuals.

The quantitative effect of iodine medication on the radioactive iodine tolerance test is clearly demonstrated in six thyrotoxic patients (Table 26). As expected, the iodine medication increased the excretion of I^{131} considerably, from the thyrotoxic range to the normal range or even beyond. Under such circumstances the radioactive iodine tolerance test is without diagnostic value. These observations are in agreement with those of Werner *et al.* (1948). The finding of a low excretion of I^{131} despite iodine medication is obviously a strong indication of thyrotoxicosis. However, this is unlikely except in very toxic patients.

Table 26. **The effect of potassium iodide on the urinary excretion of I^{131} in thyrotoxic patients.**

Case number	48 hour excretion of I^{131} during therapy per cent	Duration of therapy	Interval between cessation of therapy and I^{131}-test days	48 hour excretion of I^{131} after cessation of therapy per cent	Remarks
153	97.2	8 months	10	22.8	[1] 15 hour excretion
144	81.2	3 »	10	22.4	[2] Test done before iodine was started
163	76.4	several years	17	24.8	[3] Tests before and 2 days after operation where iodine was used
15	99.7	14 weeks	20	22.7	[4] Iodine used at an operation
179	67.4	6 »	59	8.2	[5] Calculated from in vivo measurements
3	56.7[1]			32.0[2]	[6] 72 hour excretion
181				14.5[3]	
			2	72.0	
56		8 months	6	6.4	
117			6	68.7[4]	
			34	36.7	
182		6 weeks	6	85.3	
			12	30.0[5]	
172		8 »	7	27.7	
160		several years	7	17.8	
			27	14.5	
53		3 weeks	7	24.3	
90		6 months	7	32.3	
			16	16.1	
62		3 weeks	10	7.8	
			16	9.5	
180		4 »	14	44.6	
			32	30.3	
42		15 months	14	5.2	
114		6 weeks	15	29.7[6]	
4		10 »	16	8.1	
79		4 »	28	25.2	

The duration of the iodine effect was estimated from the results of radioactive iodine tolerance tests carried out at various intervals after the cessation of iodine medication.

The effect on the tolerance test due to an elevated plasma iodide will not last more than about two days. The pharmacological effect may last longer. The present studies do not definitely establish the duration of the iodine effect, but they do provide an estimate that may be of practical value. Studies were made in 20 patients with mild to moderately severe thyrotoxicosis (Table 26). In four patients in whom the test was done two, six, six, and fourteen days, respectively, after cessation of iodide administration, the test did not indicate thyrotoxicosis. With the exception of

Case 180 the test indicated thyrotoxicosis when the interval was seven days or more. It is likely that the excretion still would have been normal after an interval of seven days in Cases 117 and 182. It may take much longer before the iodine effect completely disappears. In Case 90 the iodine effect lasted more than seven days and in Case 180 more than 14 days. Cases 160 and 62 show that the iodine effect had disappeared in seven and ten days, respectively. In Case 56 one may be fairly certain that the iodine effect was gone in six days. Thus, there are considerable variations in the duration of the iodine effect, presumably due to individual variations and differences in the severity of the disease. No correlation is apparent between the duration of iodine treatment and the length of time following cessation of therapy until the test indicates thyrotoxicosis. It may be said that previous iodide medication usually does not prevent the radioactive iodine tolerance test from indicating thyrotoxicosis for more than about two weeks, although the pharmacologic effect may last longer.

To sum up, when a patient is receiving iodide or has recently received iodide, a low excretion of radioactive iodine will indicate thyrotoxicosis as usual. A normal or high excretion cannot be used to exclude thyrotoxicosis until, after cessation of iodine therapy, repeated tolerance tests have demonstrated that the iodine effect has disappeared.

Organic iodine administration

Most of the contrast media used for the X-ray visualization of inner organs contain a large amount of iodine incorporated in organic molecules. For example, preparations such as Diodrast, Skiodan, and Priodax contain about 50 per cent iodine. Thus for a cholecystogram or a pyelogram 1—3 grams of iodine are usually administered.

Such iodine-containing dyes are known to elevate the serum protein-bound iodine (Riggs, Gildea, Man, and Peters, 1941). Riggs (1947) found that the elevation of the serum protein-bound iodine may last from several months to a year after a cholecystogram, for years after the administration of lipiodol, but only for days after a pyelogram. For a correct interpretation of the diagnostic value of the I^{131}-test it was necessary to study whether or not previous administration of contrast media containing iodine would affect the test. The results of such studies in nine patients with cholecystograms and four patients with intravenous pyelograms are presented in Table 27. In Cases 82 and N 24 the tolerance test was carried out before and after a cholecystogram. These experiments present direct evidence that the iodine-containing contrast media produce a marked increase of the urinary excretion of I^{131}. Indirect evidence is obtained from the observations in Cases 96, 101, and 170 where patients with clinical hyperthyroidism gave normal excretion values. Furthermore, the previous cholecystogram probably was responsible for the fact that Case 135 gave a higher excretion of I^{131} than is generally found in thyrotoxicosis.

From the present studies only a rough estimation can be made as to the duration

Table 27. **The effect of contrast media containing iodine on the urinary excretion of I^{131}.**

Case number	Diagnosis	48 hour excretion of I^{131} before constrast media per cent	Interval between administration of contrast media and I^{131}-test	48 hour excretion of I^{131} after contrast media per cent	Remarks
82	Thyrotoxicosis	12.6	2 days	79.5	Cholecystogram
96	»		6 »	49.6	»
N 24	Normal	80.0	19 »	97.4	»
170	Thyrotoxicosis		23 »	75.0	»
334	Rheumatoid arthritis		34 »	62.8	»
101	Thyrotoxicosis		2 months	47.5	»
135	»		3 »	43.3	»
159	»		8 »	36.6	»
105	»		9 »	19.4	»
22	»	23.3	2 days	41.7	I.v. pyelogram
			6 »	30.1	
140	»		4 »	36.3	»
136	»		9 »	9.9	»
132	»		33 »	38.0	»

of the disturbance of the iodine metabolism that is produced by a cholecystogram. The duration probably varies with the functional state of the gall bladder. It can be stated, however, that the duration is a matter of months at least. Whether the effect can last for as long as a year cannot be determined from the present studies.

The experiment in Case 22 demonstrates that an intravenous pyelogram increases the excretion of I^{131} (Table 27). The effect does not last very long, however. In Case 22 the effect was much more pronounced two days after the pyelography than four days later. In Case 136 it is likely that it had disappeared in nine days. Thus, the effect is of a few days' duration. Therefore, from the practical point of view previous pyelograms do not diminish the usefulness of the radioactive iodine tolerance test.

Although no studies were carried out concerning the effect of lipiodol, it can be predicted that it will have the same type of effect that will last for a long period of time.

The increased excretion of I^{131} following the administration of contrast media containing iodine is probably due to iodine that is split off from the organic molecule and appears in the plasma as iodide. This explanation is supported from the observation in Case 22, in whom the serum iodide concentration two days after the pyelogram was 16.8 μg. per cent as compared to the normal of 1—2 μg. per cent. The prolonged effect of gall bladder dye may well be due to repeated cycles of ab-

sorption of the dye from the gastro-intestinal tract and re-excretion into the biliary system.

In conclusion, following the administration of a dye containing iodine, a low excretion of radioactive iodine, as usual, indicates thyrotoxicosis, but a normal excretion does not exclude the disease. A cholecystogram may disturb the radioactive iodine tolerance test for a period of months, pyelograms for a period of days. Correspondingly, a normal PBI is helpful in ruling out the diagnosis of thyrotoxicosis, but an elevated PBI does not aid in establishing the diagnosis.

The Effect of Thyroid Medication

The administration of thyroid may or may not increase the urinary excretion of I^{131}. The effect probably varies with the dose and duration of the thyroid administration. There may also be individual differences.

In patients in whom thyrotoxicosis was caused by excessive ingestion of thyroid, the urinary excretion of I^{131} approached 100 per cent (Table 19, p. 67). A similar effect may also be seen in euthyroid patients who have been taking thyroid (Case 335, Table 28). While on thyroid, the I^{131}-excretion was higher than eight weeks after the cessation of therapy. This inhibiting effect on the collection of I^{131} by the thyroid is, however, not a constant phenomenon. In Case 336, who had taken 0.1 g. of U. S. P. thyroid daily for ten years, the excretion of I^{131} was about the same while taking the thyroid as it was four weeks after discontinuing therapy (Table 28).

The administration of thyroid may depress the activity of the thyroid gland

Table 28. **The effect of thyroid medication on the laboratory tests.**

Case number	Date	BMR per cent	PBI µg per cent	48 hour excretion of I^{131} in per cent	Remarks
290	7.9 '47	— 7			Carcinoma of the thyroid
	7.30 '47	—19	2.4	39.7	U.S.P. thyroid 0.1 g daily
	8.22 '47	—17		34.9	10.9 '46—7.9 '47
	10.29 '47	—10		58.1	
	11.18 '47		5.0	57.5	
335	11.10 '47	+ 3	9.4	86.7	U.S.P. thyroid 0.3—0.5 g daily
	1.13 '48	—17	5.4	66.8	for 5 years. Discontinued 11.13 '47
336	10.3 '47	—12 (9.15 '47)	3.9	71.2	U.S.P. thyroid 0.1 g daily for 10 years. Discontinued
	11.4 '47	—13	4.3	74.1	10.5 '47

(Farquharson and Squires, 1941; Riggs, Man, and Winkler, 1945). The increased excretion of I^{131} reflects this depression.

Following cessation of thyroid therapy, the gland may pass through a phase of increased avidity for iodine before it adjusts itself to normal, as is indicated by Case 290 (Table 28), who was given thyroid for nine months. During this period of increased avidity for iodine the urinary excretion of I^{131} may become lower than normal. The depression of the thyroid function in Case 290 is also reflected by the PBI and the BMR. Three weeks after discontinuation of thyroid the PBI was below normal, while ten weeks later it had risen to normal without thyroid therapy. The BMR underwent a similar adjustment.

The Effect of Thiouracil and Similar Compounds

Antithyroid drugs produce their pharmacologic effect by inhibiting the synthesis of thyroid hormone. The thiourea derivatives act by blocking the organic binding of iodine, while the primary collection of iodide by the thyroid apparently is uninhibited (Franklin, Chaikoff, and Lerner, 1944; Astwood, 1944—45; and others).

Rawson *et al.* (1944) observed that more than 55 per cent of a tracer dose of I^{131} was excreted in 24 hours by ten of eleven thyrotoxic patients receiving thiouracil (Table 4, p. 18).

This increased excretion of I^{131} during administration of thiourea derivatives was confirmed in the present study from radioactive iodine tolerance tests carried out before and during treatment with such drugs in 23 patients. The administration of the antithyroid drugs invariably increased the excretion of I^{131}.

It is also important to know the duration of this effect following discontinuation of therapy. The results of such studies in ten patients are presented in Table 29. All the patients had thyrotoxicosis. The response to the treatment varied considerably. Because of treatment with radioactive iodine, the antithyroid drugs were discontinued before a euthyroid state was reached. The results demonstrate that two weeks of treatment with propylthiouracil did not change the thyroid gland's avidity for iodine. Moreover, as long a treatment as 82 days may not change the gland's avidity for iodine, as demonstrated by Case 32. However, this patient did not respond at all to treatment. Case 127 had a good response with a fall of BMR from +34 per cent to +1 per cent and a marked clinical improvement, but the avidity for iodine did not change. The results in Table 29 also indicate that maximal collection of radioactive iodine for therapeutic purposes in thyrotoxicosis is achieved as soon as 48 hours after discontinuation of propylthiouracil therapy of short duration.

To sum up, the radioactive iodine excretion is increased by simultaneous treatment with antithyroid drugs, but following discontinuation of therapy the thyroid gland rapidly assumes the avidity for iodine that mirrors its functional state.

Table 29. The effect of propylthiouracil on the urinary excretion of I^{131} in thyrotoxic patients.

Case number	48 hour excretion of I^{131} in per cent		Period of treatment in days	First test after treatment		Second test after treatment	
	Before treatment	During treatment		Interval after treatment in days	48 hour excretion of I^{131} in per cent	Interval after treatment in days	48 hour excretion of I^{131} in per cent
45	28.9	70.7	15	2	29.7	4	27.9
53	24.3	41.1	15	2	24.0	6	20.5
57	8.5	19.6	15	3	11.1		
93	24.8	93.7	15	2	29.9	4	32.1
154	22.4	59.6	15	3	30.5		
14	7.1	32.7	17	2	7.9	4	6.4
88	14.0	57.5	19	3	10.6	5	19.0
127	34.7	39.2	40	3	33.8		
32	4.6	30.4	82	2	6.6	4	7.8
38[1]	26.3	80.2	58	2	23.6		

[1] Received methylthiouracil.

The Effect of Thiocyanate and Other Goitrogens

Thiocyanate acts on the thyroid gland by inhibiting the normal collection of the iodide ion. The effect of thiocyanate on the I^{131}-excretion has been discussed above (p. 82). The administration of thiocyanate may increase the excretion of I^{131}. Following omission of the drug after a long period of administration, the thyroid may go through a phase of increased avidity for iodine which is reflected by a comparatively low excretion of I^{131}. From the diagnostic point of view this effect is of little significance.

In animal experiments a number of other goitrogens, such as methyl cyanide and sulfonamides have been demonstrated. Cabbage and soy beans have a goitrogenic action in animals. It is not known to what extent such substances play any rôle as goitrogens in humans. Among the patients with myxedema there was one (Case 326) who had a goiter that disappeared on thyroid therapy. She had not taken thiocyanate or any other known goitrogen. It is possible that such findings may be explained by the action of unknown goitrogens. Greer and Astwood (1948) demonstrated that several types of food had antithyroid activity in humans. Vegetables were found to be more active than animal products. There were several vegetable families that were rather potent. Rutabaga was found to possess the greatest antithyroid activity. However, as much as 300 grams of a given foodstuff was necessary to produce an effect. It is, therefore, unlikely that foods in general will disturb the radioactive iodine tolerance test. It is, however, a possibility to keep in mind if a radioactive iodine tolerance test gives an unexpected result.

Resorption of Iodide from the Gastro-intestinal Tract

The resorption of iodide from the gastro-intestinal tract usually is rapid. Quetsch (1884) observed that orally-administered iodine could be demonstrated in the urine 9—18 minutes after its administration, if the person had an empty stomach. After a meal the excretion was moderately delayed.

Hamilton (1938) observed that radioactive iodine could be demonstrated in the peripheral circulation as early as 3—4 minutes following the oral adminstration of 250 mg. of sodium iodide labelled with radioactive iodine. Most of the iodide was resorbed in one hour, and the resorption was considered complete in three hours.

In the present study the I^{131}, with few exceptions, was administered to patients when fasting. That the resorption of the small amount of iodide (100 μg.) from the gastro-intestinal tract was complete is supported by the following facts:

1. In eight patients following total thyroidectomy almost 100 per cent of the administered iodine was eliminated through the urine.
2. In three patients in whom a moderately severe thyrotoxicosis was produced by excessive intake of thyroid tablets practically all the radioactive iodine was recovered in the urine.

Vomiting before the radioactive iodine has left the stomach will obviously disturb the test. However, such vomiting did not occur in the cases studied. Vomiting at a later stage during the test occurred in three patients. In Cases 69 and 79, who vomited one and a half hours after the administration of I^{131}, there was no radioactivity detectable in the vomitus. In Case 262, who vomited one hour after the administration of the I^{131}, a repeated test indicated that no radioactive iodine was lost in the vomitus.

In the present study oral administration was used because of its simplicity, and it has been found satisfactory. Intravenous administration would make the test much more impractical.

The Effect of Renal Function

In the development of a laboratory test that depends on urinary excretion the influence of renal function must be carefully considered. The radioactive iodine tolerance test is obviously affected by the ability of the kidneys to excrete iodine. This ability may be affected by normal variations, by renal disease, or indeed by the particular diseases being studied.

In normal individuals the total variation in the urinary excretion of I^{131} is composed of both the variation in the kidneys' excretion of iodine and the variation in the thyroid's collection of iodine. This total variation is not enough to detract from the

diagnostic value of the test. The variation in normal individuals was discussed in Chapter V.

The excretion of iodine by the kidneys in thyrotoxicosis is not decreased. The low excretion is due to the thyroid's increased avidity for iodine. This is established by the high excretion of I^{131} when larger doses of iodine (I^{127}) are given and by the almost complete excretion of I^{131} in thyrotoxicosis factitia. Furthermore, studies of the renal function in thyrotoxicosis with phenolsulfonphthalein tests (Lerman and Brogan, 1932) or urea clearance tests (Bartels, 1938) demonstrated that the kidney function in thyrotoxicosis was not depressed.

There is the possibility instead that the renal excretion of iodine is increased in thyrotoxicosis. There is no good evidence on this point, but Corcoran and Page (1947) observed in two patients with thyrotoxicosis that the renal blood flow, glomerular filtration, and tubular secretion of diodrast were increased but not in proportion to the increase of BMR. These observations suggested that thyrotoxicosis was not associated with renal vasodilatation comparable to that which occurs in the extrarenal circulation. In any event, an increase in the iodine excretion would tend to bring the excretion values in thyrotoxicosis nearer the normal. The results of the present investigation demonstrate that if there is an increase in renal excretion of iodide in thyrotoxicosis it does not interfere with the usefulness of the radioactive iodine tolerance test.

Several decades ago it was demonstrated that the urinary excretion of iodine after the administration of 0.5 g. potassium iodide was delayed in renal insufficiency (Schlayer and Takayasu, 1910; and others). Nyiri (1925) found that the excretion of iodide in a two-hour test period after the administration of 1 g. sodium iodide was decreased in kidney diseases. In these early studies, based on chemical methods, the doses of iodine were so much larger than those used for the present radioactive iodine tolerance test that the results are not comparable. However, Hamilton and Soley (1939) observed that the urinary excretion of a labelled dose of 14 mg. of iodide was delayed in one patient with renal damage.

Thus, it became necessary to determine whether the presence of renal damage would affect the urinary excretion of the minimal dose of iodine (100 μg.) that was administered for the radioactive iodine tolerance test.

Ten patients with various kidney diseases were studied. The results are presented in Table 30. None of the patients had any symptoms or signs of hyperthyroidism. The BMR was determined in six of the patients. All BMR's were rather low. The two lowest BMR's were —26 and —27 per cent. These patients also had subnormal serum protein-bound iodine values. None of them, however, exhibited any clinical signs of myxedema.

The radioactive iodine excretion was disturbed in most patients, probably in all. In eight patients the total 48-hour I^{131}-excretion was in the thyrotoxic range and in the remaining two patients the excretion was in the low normal range. In one of these two patients the excretion for the second day was higher than that observed

Table 30. **The laboratory tests in patients with renal disease.**

Case number	Age Sex	Diagnosis	Blood pressure	NPN mg per cent	Phenolsulfonphthalein excretion in 2 hours[1] per cent	Cholesterol mg per cent	BMR per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent			Uptake of I^{131} by the thyroid after 48 hours, per cent
									0—24 hours	24—48 hours	Total in 48 hours	
338	43 ♂	Acute nephritis	140/80	43	20	236		5.1	22.7	9.4	32.1	
339	69 ♀	Chronic pyelonephritis + Rheumatoid arthritis + ? Vitamin D intoxication	140/70	68	24			3.5	23.5	11.4	34.9	20.6
340	21 ♀	Chronic glomerulonephritis	115/95	140		179	—10		1.3	1.9	3.2	32.3
341	62 ♂	Chronic glomerulonephritis with nephrosis	155/100	165		287	—19	2.0	2.7	1.7	4.4	72.4
342	33 ♂	Chronic glomerulonephritis with nephrosis	140/95	32			—27	2.2	35.0	11.4	46.4	43.2
343	30 ♂	Amyloid nephrosis	100/60	75	< 5	329	—26	1.9	15.2	1.7	16.9	70.7
344	55 ♂	Nephrosclerosis	230/110	190		162		2.0	5.5	3.9	9.4	—
345	51 ♀	»	225/150	62	22		—11	5.4	19.8	7.9	27.7	42.5
346	41 ♂	»	270/150	22	45	147	—15		23.2	13.2	36.4	65.1
347	60 ♂	»	125/70	68				3.9	29.0	21.0	50.0	

[1] Normal value: ≥ 55 per cent in 2 hours ROURKE, MACLACHLAN, and BUTLER (1946).

in normal subjects. In four of the eight patients with the total 48-hour excretion within the thyrotoxic range the second-day excretion values were generally higher than those observed in thyrotoxicosis. In the four remaining cases the I^{131}-excretion gave results characteristic of thyrotoxicosis.

The present material is small. A larger number of patients with kidney diseases need to be studied to determine how severe the renal damage has to be in order to bring the 48-hour excretion of I^{131} below the normal range. At present it can only be stated that in the presence of renal damage the determination of the 48-hour excretion of I^{131} is unsatisfactory as a diagnostic test in thyrotoxicosis. It is true, however, that in five of ten patients with renal damage it was possible to tell from the urinary excretion data that thyrotoxicosis was not present.

For diagnostic use of the radioactive iodine tolerance test it is necessary to know how often thyrotoxicosis and renal disease appear together. SELVAAG (1948) found this combination in only two per cent of thyrotoxic patients. In the present study there appeared only one patient (Case 186) in whom thyrotoxicosis was probably

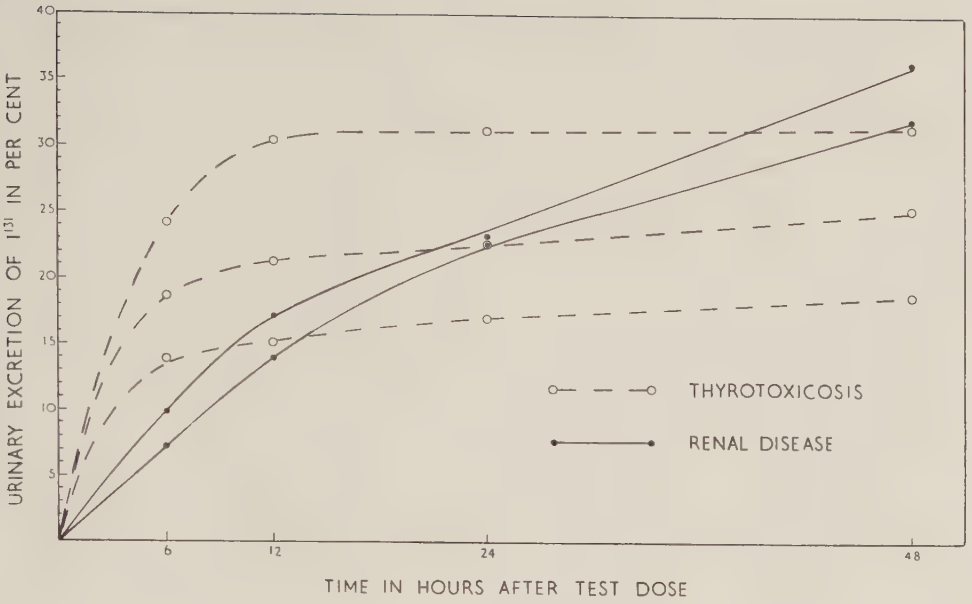

Fig. 17. Cumulative excretion curves of I^{131} in thyrotoxicosis and renal disease.

associated with renal insufficiency (Table 34, p. 128). Furthermore, there was only one patient (Case 385) in whom a disease simulating thyrotoxicosis was associated with apparent renal damage (Table 41, p. 152). These observations indicate that misleading values because of kidney disease will not appreciably limit the clinical value of the tolerance test.

In two patients excretion curves were obtained. Although the total excretion was below normal, the shape of the curves (Fig. 17) indicated that the low excretion was not due to thyroid hyperfunction but to the renal damage. It is possible that the determination of the excretion rate from the slope of such curves will differentiate between thyrotoxicosis and renal disease. Further studies are necessary, however.

The question arises whether this interference due to kidney disease might be overcome by direct measurement of the total collection of I^{131} by the thyroid. When the radioactive iodine has entered the blood stream there are fundamentally only two organs that compete for the radioactive iodine, the thyroid and the kidneys. If the kidneys do not excrete iodine at a normal rate, the thyroid will have more time to collect I^{131}. Assuming that the thyroid collection rate is constant, then the total thyroid collection will become greater than with normally functioning kidneys. *In vivo* measurements of the total amount of I^{131} collected by the thyroid in 48 hours were carried out in seven patients. In three of these patients the thyroid had collected as much I^{131} as in thyrotoxic patients. Thus, it is apparent that the estimation of the total amount of I^{131} collected by the thyroid after 48 hours does not differentiate between thyrotoxicosis and renal disease. Corresponding to what has been

said about excretion curves, it may be possible to distinguish between thyroid hyperfunction and renal disease by determining the thyroid collection rate from repeated *in vivo* measurements.

It is not certain, however, that the high collection of I^{131} in some of these patients was entirely a result of the renal damage. The two patients with the highest thyroid collection of I^{131} (Cases 343 and 341) had BMR's of —26 and —19 per cent, respectively. Their PBI's were below normal, 1.9 μg. per cent and 2.0 μg. per cent, respectively. These laboratory findings thus were consistent with myxedema, of which the patients presented no symptoms whatsoever. The low PBI may be due to losses of thyroid hormone in the urine. It is conceivable that the high collection of I^{131} indicates that these thyroids were manufacturing thyroid hormone at a rapid rate, but that due to losses of hormone in the urine there was a drop in the level of the PBI. Further studies of this problem are necessary.

In conclusion, the urinary excretion of I^{131} may be lower than normal in patients with kidney disease. In the presence of renal damage a subnormal excretion may or may not indicate thyrotoxicosis. The determination of the excretion rate of radioactive iodine will probably differentiate between thyrotoxicosis and renal failure. The disturbance of the radioactive iodine tolerance test by kidney disease is of little significance from the clinical point of view.

The Effect of Congestive Heart Failure

In the diagnosis of thyrotoxicosis the problem occasionally arises whether congestive failure is due to thyrotoxicosis or to organic heart disease or to a combination of both. Thus, it was necessary to determine whether or not the disturbed fluid balance in congestive heart failure would detract from the value of the radioactive iodine tolerance test.

One would anticipate that a larger than normal fraction of the administered I^{131} would be retained in the increased extracellular fluid in congestive failure. Such a retention in a euthyroid individual might produce a low excretion of I^{131} comparable to that observed in thyrotoxic patients.

This problem of an increased retention of radioactive iodine was studied in twelve patients with congestive failure. The results are presented in Table 31. Eight patients were thyrotoxic and four were euthyroid. The congestive failure was of mild to moderately severe degree. In one of the thyrotoxic patients (Case 117) the peripheral edema probably was due to varicose veins.

The amount of I^{131} collected by the thyroid plus that excreted in the urine in 48 hours varied between 91.3 and 112.0 per cent with an average of 99.0 per cent (Table 31). These results indicate that after 48 hours the I^{131} is either collected by the thyroid or excreted in the urine even in congestive failure. The results do not seem to be different from what is observed in patients without congestive failure. As the

Table 31. **The effect of congestive failure on the radioactive iodine tolerance test in hyperthyroid and euthyroid patients.**

Case number	State of thyroid function	48 hour urinary excretion of I^{131} per cent	Uptake of I^{131} by the thyroid after 48 hours per cent	Total amount of I^{131} in urine and thyroid per cent
37	Hyperthyroid	18.0	94.0	112.0
54	»	13.6	80.5	94.1
59	»	22.5	72.0	94.5
73	»	18.8	86.7	105.5
102	»	12.1	88.3	100.4
117	»	68.7[1]	25.4	94.1
127	»	35.1	61.6	96.7
129	»	25.4	74.1	99.5
231	Euthyroid	64.9		
233	»	63.3	38.2	101.5
334	»	62.8	28.5	91.3
337	»	67.9	36.9	104.8
353	»	62.6		
354	»	65.9		
355	»	66.5	27.1	93.6
358	»	53.1		
362	»	62.1		

[1] 6 days after administration of ordinary iodine.

in vivo measurement method was standardized on the basis of urinary excretion data, one would obtain a value below 100 per cent if there were more I^{131} retained in the peripheral tissues in congestive failure than in patients with undisturbed fluid balance. From these studies no conclusion can be drawn as to whether the presence of edema decreased the urinary excretion of I^{131} and consequently increased the thyroid collection. It may be said, however, that such an effect, if present, would be small and probably without practical significance. This thesis is supported by the fact that in nine patients with congestive failure without thyrotoxicosis the urinary excretion of I^{131} was within normal limits (Table 31). The average 48-hour excretion of 63.2 per cent did not differ significantly from the normal average of 65.9 per cent. These observations show that the presence of congestive heart failure is unlikely to diminish the clinical value of the radioactive iodine tolerance test.

The possibility cannot be excluded, however, that the presence of congestive failure may decrease the urinary excretion of I^{131} to some extent. The magnitude of such a probable decrease is indicated by Case 65. This was a patient with thyrotoxicosis and severe congestive failure. The excretion of I^{131} was 6.5 per cent when the patient was in severe cardiac failure with massive edema (weight 56.0 kg.). When she was relieved from her decompensation (weight 47.3 kg.) the excretion

of I^{131} was 13.0 per cent. Her thyrotoxicosis had also improved in the meantime. The higher excretion in the second test was probably due to a combination of the disappearance of the edema and an abatement of thyrotoxicosis. It should be noted, however, that the difference between the two tests is not greater than might appear in duplicate tests.

The patients discussed here all had rather stable edema. The effect of the disturbed fluid balance on the radioactive iodine tolerance test may be greater during the development of edema. Unfortunately no such studies could be carried out.

The results obtained in this group of patients with edema from congestive heart failure also indicate that the edema *per se* is not responsible for the very low excretion of I^{131} in certain patients with renal disease.

If there is any doubt as to the validity of the I^{131}-test in a patient with congestive failure, the test should be repeated when the patient is freed of decompensation.

The results demonstrate that in congestive failure no increased amount of I^{131} remains in the extracellular fluid after 48 hours. The normal excretion of I^{131} in patients with congestive heart failure without thyrotoxicosis shows that the presence of mild to moderately severe congestive failure does not interfere with the radioactive iodine tolerance test as a measure of thyroid activity.

The Effect of Radiation from I^{131}

A possible objection to the use of radioactive iodine in the study of thyroid disease is that the presence of radiation may influence the results or may produce damage to body tissues, particularly to the thyroid.

It was previously demonstrated that within wide limits the size of the dose of I^{131} does not affect the results of the radioactive iodine tolerance test (see p. 33).

The size of the dose of I^{131}, however, must be considered from the point of view of producing radiation damage.

In this investigation 100 μc. of I^{131} were generally used for diagnostic studies. If one assumes that the I^{131} taken up by the thyroid stays in the gland until it has disintegrated completely, such a dose will expose the thyroid to about 150 roentgen-equivalent-physical units (reps) in about 40 days, assuming an uptake of 30 per cent and a thyroid weight of 20 grams. This value represents a maximum, as part of the radioactive iodine leaves the thyroid before it has disintegrated. The dosage is directly proportional to the concentration expressed as μc. per unit weight. The same total uptake in a gland of the double size will thus produce half as large a dose of radiation. It is highly unlikely that this amount of radiation will damage the thyroid. In diagnostic X-ray work the patients are exposed to comparable radiation doses. For example, a gastro-intestinal X-ray series including fluoroscopy will expose the patient to about 50—75 roentgens during a short period of time.

Furthermore, in experiments on animals no damage to the thyroid was produced

with doses of I^{131} that gave a total radiation of about 1700 reps to the thyroid (Skanse, 1948 c). It should be admitted, however, that there may be great species differences in sensitivity to radiation.

Doses of 100 μc. of I^{131} or even larger have been used in humans by a number of investigators for several years without any report whatsoever of untoward effects. In tissues other than the thyroid the radiation hazard does not need to be considered for doses of 100 μc. of I^{131}.

Naturally it would be still safer to administer even smaller doses of I^{131}. With the methods employed in this study it is entirely sufficient to use 10 μc. of I^{131} for the determination of the urinary excretion. There is little doubt that the methods can be refined to permit urinary excretion studies with 1—2 μc. of I^{131}. Such a dose would keep the radiation exposure of the thyroid below the 0.1 equivalent roentgen per day which is considered harmless for an indefinite period of time. For quantitative *in vivo* measurements of the collection of I^{131} by the thyroid the present available methods are too insensitive for even 10 μc. of I^{131}.

As the possibility of radiation damage exists in the use of I^{131}, it is evident that the previously discussed standardization of the employed I^{131} in absolute units is a necessary precaution to prevent injuries.

Chapter VIII

THE USE OF THE RADIOACTIVE IODINE TOLERANCE TEST IN THE DIAGNOSIS OF THYROTOXICOSIS

There are few diseases in internal medicine that are more easily recognized than classic thyrotoxicosis. The typical history and the characteristic clinical findings leave little doubt as to the diagnosis. However, few diseases present such a variable clinical picture as does thyrotoxicosis. Furthermore, there is no symptom or sign pathognomonic of thyrotoxicosis.

Hyperfunction of the thyroid gland produces symptoms from several organ systems. These symptoms may be combined in a great many ways, producing a variety of clinical types of thyrotoxicosis. Some of the types that appear more frequently are relatively well defined but may still present diagnostic problems. More unusual types are easily overlooked. In a considerable number of patients one or more of the cardinal symptoms are missing. In such atypical cases of thyrotoxicosis the diagnosis may present great difficulties. In other patients the clinical picture of thyrotoxicosis is hidden by complicating diseases such as cardiovascular disorders. There is undoubtedly a considerable number of patients with thyrotoxicosis in whom a clinical diagnosis cannot be made with reasonable certainty. Different laboratory methods have been devised to facilitate the diagnosis of thyrotoxicosis in such equivocal cases.

The determination of the basal metabolic rate has been the classical laboratory method in the diagnosis of thyrotoxicosis. It has, however, two important limitations. In the first place, the BMR is not always elevated in thyrotoxicosis. The reason for this phenomenon is probably that such patients when healthy have BMR's of —15 per cent to —20 per cent. When they develop thyrotoxicosis the BMR will rise, but not enough to give a value above the accepted normal limit. From the literature as well as from the present study it is apparent that such patients are not unusual. Furthermore, the normal BMR's appear particularly in patients in whom the diagnosis of thyrotoxicosis is difficult to make on clinical grounds. It is true that a normal basal metabolic rate makes the diagnosis less likely, but *a normal BMR cannot be used to exclude thyrotoxicosis.*

The second limitation of the BMR is due to the fact that a number of extrathyroidal diseases are capable of producing an elevated BMR. This is especially troublesome

in diseases that in themselves may simulate thyrotoxicosis, such as cardiac disease and essential hypertension.

In the following discussion the diagnostic value of the radioactive iodine tolerance test in thyrotoxicosis will be considered, particularly in patients in whom the diagnosis could not be established on clinical grounds at the time of study. In these cases the BMR was often normal, and even when elevated, it was not reliable because of complicating diseases, or it was so slightly elevated that there was still doubt as to the diagnosis.

As has been pointed out in Chapter VI, the diagnoses in the present study in all doubtful cases were determined by the clinical picture, particularly the clinical course subsequent to the time of study. However, a diagnostic test is of no value when the patient's entire illness is concluded, and for purposes of evaluating the radioactive iodine tolerance test it was helpful to consider how often is was of value in establishing the diagnosis before the future course clarified the situation. Thus, although it has been necessary for methodological purposes not to include the results of the radioactive iodine tolerance test in determining in which diagnostic group the patient is placed, nevertheless in practice the result of this test often helped in making a diagnosis before the course of the illness definitely established it.

Since one of the objectives of the present study is to compare the value of different laboratory methods for the diagnosis of thyrotoxicosis, it was considered convenient to divide the thyrotoxic patients who presented diagnostic problems into two groups according to the value of the basal metabolic rate, i.e., patients with elevated BMR and patients with normal BMR.

Diagnostic problems have arisen particularly in three categories:

1. mild thyrotoxicosis
2. atypical thyrotoxicosis
3. thyrotoxicosis complicated with other diseases.

Naturally this classification is somewhat arbitrary. In several instances it was a combination of various factors that together formed the diagnostic problem. The classification will facilitate the discussion but will not interfere with the results.

Eighty-one cases are included in the category of patients with thyrotoxicosis with diagnostic problems (Cases 95—175). The most important clinical and laboratory data are presented in Tables 32 and 33. A few cases will be reported in more detail in order to illustrate certain remarkable clinical features or diagnostic problems.

Presentation of data

The limited space does not permit the publication of all clinical data. Those presented are selected particularly to illustrate the symptoms and signs of thyrotoxicosis. Most of the data are self-explanatory, but a few comments may be helpful for further interpretation.

Intolerance to heat: This symptom is of great value in a place like Boston where the hot, humid summers are really trying for borderline thyrotoxic patients.

Nervousness: By nervousness is meant the characteristic labile, excited condition of thyrotoxicosis with overactivity, irritability, and emotional instability. It should be admitted that certain nonthyrotoxic patients, especially those with anxiety neurosis, did not show all these characteristics. The term "nervousness" was used for these patients also, for lack of any better term.

Tremor: This was observed in the outstretched hands.

Thyroid size and type: The size of the thyroid gland is given in comparison with the size of the normal gland. Thus, for example, the figure "3" means three times normal size. The estimation of the size was done by palpation. Usually the size, as given in the tables, represents the average of the estimates made by several members of the Thyroid Clinic of the Massachusetts General Hospital. Obviously such a method is only approximate. The tables indicate whether the thyroid was felt to be nodular or diffuse. It should be admitted that this clinical observation sometimes proved to be wrong at operation. The most common error was that a gland, judged as diffusely enlarged, was found to be nodular. The opposite also occurred.

Eyes: The presence of exophthalmos was estimated directly and usually also measured by either Luedde's or Herthel's exophthalmometer.

Heart: The enlargement of the heart was always checked by X-ray. The pulse rate represents the average of the readings for several days for the hospitalized patients. For out-patients the pulse rate usually represents a single reading. The presence of fibrillation was checked by electrocardiogram.

Basal metabolic rate: The figures represent averages as discussed on p. 45.

Serum protein-bound iodine: In many patients with diagnostic problems repeated PBI's were taken. In such cases the figures represent the average.

Thyrotoxicosis with Elevated Basal Metabolic Rate (> + 20 per cent)

This group consisted of 42 patients (Cases 95–136). The BMR was only slightly to moderately elevated in most patients. Greater elevations occurred almost exclusively in patients in whom complicating diseases were at least partly responsible for the increased BMR.

1. Patients in whom the history and clinical findings were vague but rather suggestive of thyrotoxicosis

This type of patient is represented by Cases 95—101 (Table 32). In all seven patients the disease was very mild. The BMR in every patient was below +30 per cent. Although the symptoms were consistent with thyrotoxicosis they were not altogether convincing. Diarrhea was an outstanding symptom in Case 100 in spite of the mild thyrotoxicosis. The thyroid gland was only slightly enlarged in Cases 98 and 101, only twenty grams of thyroid tissue being removed in the latter case.

The urinary excretion of I^{131} was less than normal in five of the patients. In Cases 96 and 101 the excretion was in the low normal range (in the zone between -2σ and -3σ of the normal mean). In view of the fact that a cholecystogram had been

performed six days previously (Case 96) or two months previously (Case 101), these excretion values were considered to be low enough to support the diagnosis of thyrotoxicosis despite their borderline character.

The elevated PBI in Case 101 may have been entirely caused by the previous cholecystogram and could therefore not be used as support of the diagnosis of thyrotoxicosis. The fact that the PBI fell from 14.1 μg. per cent to 9.2 μg. per cent in five weeks without any change in the clinical picture indicated that the elevation of the PBI was at least partly due to the administration of the gall bladder dye. Following a cholecystogram an elevated PBI cannot be taken as evidence for thyrotoxicosis.

It should be observed that in Case 98 the PBI was normal, while the radioactive iodine tolerance test indicated thyrotoxicosis.

In the above group of patients the diagnosis of thyrotoxicosis could be made from the clinical picture and the basal metabolic rate. The results show that the radioactive iodine tolerance test may be used to confirm the diagnosis of thyrotoxicosis in clinically very mild cases if the slightly elevated BMR is not considered as sufficient evidence.

2. Patients in whom the history and/or the clinical findings were not characteristic of thyrotoxicosis

Twenty-four patients were referred to this group (Cases 102—125). The clinical and laboratory data are summarized in Table 32. These patients presented a spectrum of diagnostic problems.

The atypical history produced the diagnostic difficulties in Cases 102–109. The thyrotoxicosis was rather mild in all eight patients. The highest BMR was +37 per cent. There was somtimes a complete lack of thyrotoxic symptoms (Case 102). In other patients only single suggestive symptoms such as sweating (Case 104) or weight loss (Case 108) were present. The gain in weight in Cases 107 and 109 was certainly atypical for thyrotoxicosis. In Case 105 the history was so confused with psychoneurotic symptoms that it was impossible to interpret. In all these patients the radioactive iodine tolerance test indicated thyrotoxicosis. The possibility of thyrotoxicosis factitia was raised in Case 106 but was excluded because of the low excretion of I^{131}.

A most extraordinary history of thyrotoxicosis was presented by the following patient:

Case 103. This 29-year-old woman complained chiefly of swelling of the feet and calves of five weeks' duration. The swelling was transitory at first but soon became constant. It subsided incompletely during the nights. The patient also noted puffiness of her eyes. She had developed slight dyspnea and palpitation on climbing stairs. She was intolerant to extremes of both heat and cold, but did not perspire excessively. There was no weight loss, increased appetite, nervousness, shakiness, or swelling of the neck. The last two menstrual periods had lasted only one day instead of the usual five. Except for the edema she had felt well.

Table 32. Clinical and laboratory data in thyrotoxic pati

Case number	Age Sex	History										Physical examination								
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes			Heart		Pulse rate	Blood pressure
															Exophthalmos	Lid lag	Lid retraction	Enlargement	Fibrillation		
95	36 ♀	0	+	0	0	0	+	+	0	+	+	2, N, s	w, m	+	0	0	+	0	0	80	100/60
96	52 ♀	+	0	0	+	0	0	0	0	+	+	2, D, f	w	+	0	+	0	0	0	86	150/90
97	33 ♀	+	+	+	+	+	+	0	0	+	+	2, D, s	w, m	+	0	0	0	0	0	100	135/70
98	59 ♂	+	+	+	+	0	0	0	0	+	+	1½, D, s	w, m	+	0	+	+	0	0	78	140/80
99	25 ♀	+	+	+	+	+	0	+	0	0	+	2, D, f	w, m	+	0	0	0	0	0	94	100/60
100	48 ♂	+	+	0	0	+	+	0	0	0	0	1½—2, D, f	n	+	+	0	0	0	0	120	140/65
101	59 ♀	0	0	+	+	+	+	+	0	+	+	1½, N, f	w, m	+	0	0	0	0	0	84	140/80
102	55 ♀	0	0	0	0	0	0	+	0	0	0	4—5, D, s	w, m	+	0	0	0	+	+	120	160/70
103	29 ♀	0	0	0	0	0	+	0	0	0	0	1½—2, D, f	w	+	0	0	0	0	0	84	120/75
104	23 ♀	0	0	0	+	0	0	0	0	0	0	2½, D, f	w, m	+	0	0	0	0	0	100	130/70
105	57 ♀	0	0	+	0	+	+	0	0	+	0	1½, D, s	w, d	+	0	0	0	0	0	120	200/80
106	45 ♀	0	+	+	+	0	0	0	0	+	+	1½, D, s	w, m	+	+	+	+	0	0	100	130/80
107	30 ♂	0	+	+	+	0	0	0	0	0	0	2, D, s	w, m	+	0	0	0	0	0	100	115/70
108	64 ♀	+	0	0	0	0	0	+	0	0	0	2, N, f	w, m	+	0	0	+	0	0	110	160/80
109	37 ♀	0	+	+	+	+	0	+	+	0	0	1½, D, f	w, m	+	0	+	+	0	0	100	130/85
110	45 ♀	+	+	+	0	+	+	0	0	+	0	not palpable	w, m	+	0	+	0	+	0	110	120/65
111	55 ♀	+	0	+	+	+	+	0	0	+	+	1, D, s	n	+	0	0	0	0	0	90	140/80
112	42 ♂	+	+	+	+	0	0	0	0	+	+	1, D, s	w, m	+	0	+	0	+	0	104	125/80
113	75 ♀	0	0	+	+	0	+	0	0	+	0	1½, N, f	n	0	0	0	0	0	0	100	185/80
114	52 ♀	+	0	+	0	+	+	0	0	+	0	1½—2, D, f	w	0	+	0	0	0	0	116	170/110
115	70 ♀	+	+	+	+	0	+	0	0	0	0	2, N, s	c, m	0	0	0	0	0	0	84	160/80
116	38 ♀	0	0	0	0	+	0	+	0	+	0	2½, D, s	m	0	0	0	0	0	0	72	130/70
117	52 ♂	0	0	0	+	0	0	0	0	0	0	1½, N, f	w, m	+	0	+	0	0	0	80	150/100
118	55 ♀	0	0	+	+	0	+	+	0	+	0	1½, N, f	w	+	0	0	0	+	0	76	135/85
119	36 ♀	+	+	0	+	+	+	0	0	+	0	2, N, f	w, m	+	0	0	+	0	0	80	125/75
120	53 ♀	+	0	0	0	0	+	0	0	0	0	1½, D, s	m	+	0	0	0	0	0	100	150/85
121	54 ♀	+	0	+	+	0	0	0	0	+	+	1—1½, D, f	m	+	0	0	0	0	0	120	160/80
122	55 ♀	+	0	0	+	+	+	0	0	0	0	2, N, s	n	0	0	0	0	0	0	98	120/60
123	71 ♂	+	+	0	0	+	+	0	0	0	+	1, D, f	n	+	0	0	0	0	0	88	150/70
124	51 ♂	+	0	0	0	+	0	+	0	+	0	1½, N, s	n	+	0	0	0	0	0	80	130/100
125	44 ♀	+	0	0	0	+	0	0	0	+	+	2, D, f	n	+	0	0	0	0	0	100	125/70

elevated BMR and presenting diagnostic problems.

Laboratory findings					Complicating disease	Treatment	Result of treatment	Remarks
BMR per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent						
		0—24 hours	24—48 hours	Total in 48 hours				
+27	8.3	40.6	0.6	41.2		op.	+	
+26		47.1	2.5	49.6		KI	+	Cholecystogram 6 days before I^{131}-test.
+25		40.5	2.7	43.2		KI	+	
+24	7.3	34.3	0.8	35.1		I^{131}	+	
+22	11.4	17.0	3.0	20.0		op.	+	
+21	11.9	27.2	2.2	29.4		I^{131}	+	
+27	9.2	45.7	1.8	47.5		op.	+	Cholecystogram 2 months prior to study. Toxic adenoma.
+37		11.1	1.0	12.1	Congestive failure	I^{131}	+	Recurrent thyrotoxicosis.
+27	10.8	19.8	1.4	21.2	Fibroma and endometriosis of ovary	op.	+	
+30	16.7	10.3	2.5	12.8		PTU	+	
+23	11.4	19.0	0.4	19.4		I^{131}	+	
+29	9.0	23.1	1.6	24.7		TU	+	
+36		17.7	0.7	18.4		PTU	+	
+37	6.7	36.1	2.6	38.7		op.	+	
+27	9.4	36.1	0.8	36.9		op.	+	
+50	13.2	21.8	1.0	22.8		PTU	+	Recurrent thyrotoxicosis.
+21	8.7	30.8	1.4	32.2	Bronchogenic cyst	0	+	Spontaneous remission.
+63	11.9	8.2	9.3	17.5		op.	+	Thyrotoxic myopathy.
+34	8.4	58.0	8.1	66.1	Diabetes mellitus	op.	+	
+54	10.8	15.1				TU	+	
+32	10.6	31.4	6.2	37.6	Coronary heart disease	I^{131}	+	
+30		24.2	0.0	24.2		I^{131}	+	
+24		35.1	1.6	36.7		op.	+	Toxic adenoma.
+28	11.5	32.2	1.3	33.5		op.	+	Toxic adenoma.
+25	10.9	23.3	0.6	23.9		op.	+	
+50	17.9	20.3				I^{131}	+	
+32		26.8	1.1	27.9	Chronic bronchiectasis	I^{131}	+	
+31	11.5	13.8	1.3	15.1		op.	+	
+41		26.8	2.6	29.4		PTU	+	
+24	11.0	35.3	6.5	41.8	Chronic alcoholism + ? Cirrhosis of the liver	PTU	+	
+29		29.2	1.2	30.4	Psychosis	op.	?	

(Cont.).

Case number	Age Sex	History										Physical examination									
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes			Heart		Pulse rate	Blood pressure
															Exophthalmos	Lid lag	Lid retraction	Enlargement	Fibrillation		
126	66 ♂	+	+	0	0	0	0	0	+	+	0	1½, N, s	n	+	+	0	+	0	0	106	215/105
127	47 ♀	+	0	0	0	+	+	0	0	+	0	2, D, s	n	0	0	0	0	+	+	90	140/80
128	45 ♀	+	0	+	+	0	0	+	0	+	+	1½, D, s	w, m	+	0	0	0	+	0	114	170/70
129	55 ♀	+	+	+	+	+	+	0	0	+	+	2–2½, D, s	w, m	+	0	0	0	+	0	120	220/90
130	58 ♀	+	0	0	+	+	+	0	0	+	+	1, D, s	w, m	+	0	0	0	+	+	76	240/125
131	68 ♂	+	+	0	0	+	0	0	+	+	+	1, D, s	w, d	+	+	+	+	+	0	80	
132	64 ♀	+	+	+	+	+	0	+	0	+	+	2, N, s	w, m	+	0	0	0	+	0	84	155/85
133	65 ♀	+	0	0	0	+	+	0	0	0	+	2, N, f,	w, d	+	0	0	0	0	0	130	150/75
134	55 ♀	0	0	0	0	+	+	0	0	+	0	1½, D, s	w, m	0	0	+	+	+	0	72	195/100
135	67 ♀	+	0	0	0	+	+	+	0	+	0	2½, N, s	w, m	+	0	0	0	0	0	90	115/60
136	48 ♀	0	0	+	0	0	0	0	0	+	0	1½, D, s	n	+	0	0	+	+	0	80	200/100-130/80

The physical examination was negative except for moderate pitting edema of ankles and feet, increased warmth of skin, minimal tremor of the extended fingers, a smooth and firm thyroid about 1 ½—2 × normal size, puffiness of the eyelids, and a mass in the left pelvis.

The Hgb was 10.1 g. per cent and the RBC was 3,200,000. The blood proteins were 5.89 g. per cent with 4.16 g. per cent albumin and 1.73 g. per cent globulin. BMR's were +24, +28, and +30 per cent. PBI's were 9.7 and 11.9 μg. per cent. The 48-hour excretion of I^{131} was 21.2 per cent.

After removal of 22 grams of thyroid tissue her edema soon disappeared, and her periods became normal. A fibroma of the ovary with associated endometriosis was removed at a later operation.

Remarks:—From the history and clinical findings it was not possible to make a diagnosis of thyrotoxicosis. The I^{131}-excretion suggested thyrotoxicosis as did the PBI. The possibility of Struma ovarii was ruled out by *in situ* measurements as all the I^{131} was concentrated in the neck. The subsequent course demonstrated that the laboratory tests had been correct. In this patient the thyrotoxicosis manifested itself in an unusual way with edema as the major symptom.

In other patients the history was suggestive of thyrotoxicosis, but the clinical

Laboratory findings					Complicating disease	Treatment	Result of treatment	Remarks
BMR per cent	PBI μg per cent	Urinary excretion of I^{131} in per cent						
		0—24 hours	24—48 hours	Total in 48 hours				
+22		29.2	2.4	31.6	Hypertensive cardiovascular disease	KI TU	?	Died from coronary thrombosis.
+34	6.9	32.6	2.5	35.1	Rheumatic heart disease with congestive failure	I^{131}	+	
+60	16.4	8.9	1.2	10.1	Paralysis agitans	op.	+	
+97	10.3	24.0	1.4	25.4	Rheumatic heart disease with congestive failure	I^{131}	+	Recurrent thyrotoxicosis.
+22	9.4	36.8	1.3	38.1	Hypertensive cardiovascular disease	op.	+	Toxic adenoma.
+30	14.0	10.3	0.8	11.1	Carcinoma of the rectum	KI	+	
+58		34.9	3.1	38.0	Masculinizing syndrome	I^{131}	+	
+39	10.3	24.9	0.7	25.6	Carcinoma of the lung and pleura	KI	+	
+61		7.5	0.9	8.4	Hypertensive cardiovascular disease	op.	+	
+28	13.4	40.5	2.8	43.3	Chronic cholecystitis with biliary cirrhosis	PTU	+	Cholecystogram 3 months prior to study.
+28	15.0	9.4	0.5	9.9	Essential hypertension	op.	+	

findings were atypical or unimpressive (Cases 110—113, Table 32). In Case 110 there was no thyroid palpable, but the low excretion of I^{131} as well as the high concentration of I^{131} in the neck confirmed the diagnosis of thyrotoxicosis. An X-ray showed a deep-seated mass in the lower neck.

The diagnosis of thyrotoxic muscular atrophy was facilitated by the radioactive iodine tolerance test and the PBI in Case 112 in whom no goiter was palpable, and in whom a generalized muscular atrophy, predominantly of the shoulder girdle, was a striking feature in the clinical picture. The value of the radioactive iodine tolerance test and the PBI in the recognition of thyroid hyperfunction in atypical cases is clearly illustrated by the following case report:

Case 111. This 55-year-old woman complained chiefly of weight loss and nervousness. Seven years earlier she had had a radical mastectomy for carcinoma of the breast. She was followed carefully and showed no evidence of metastases. In the three months before admission she lost about six kg. despite a fair appetite, felt very fatigued, became nervous, and noted tremor of her hands. She developed increased intolerance to heat and perspired more than usual. Occasionally she was bothered by palpitation.

The physical examination was negative except for a fine tremor of the hands and a pulse rate of 90. The thyroid was not enlarged. X-rays of the chest revealed a soft tissue mass in the region of the aortic arch. The mass was well defined and was about 4 cm. in diameter.

BMR's were +15, +27, and +21 per cent. PBI was 8.7 μg. per cent. The 48-hour excretion of I^{131} was 32.2 per cent.

She was followed without treatment. Three months later her BMR was +6 per cent. Five months later her BMR was +3 per cent, she had gained 4 kg. in weight and felt much improved. At this time the I^{131}-excretion was 63.3 per cent. She was operated upon because of the mediastinal mass which was found to be a bronchogenic cyst.

REMARKS:—This patient presented a diagnostic problem. Weight loss and fatigue were the dominant symptoms in her history. In view of the fact that this patient was previously operated on for carcinoma of the breast, it seemed probable that her symptoms were due to metastatic malignancy. The mediastinal mass strongly supported this possibility. Her history was also compatible with thyrotoxicosis, but the clinical picture was not convincing. The I^{131}-excretion favored thyrotoxicosis as did the PBI. In retrospect this diagnosis was further supported by the fact that the I^{131}-excretion returned to normal when her symptoms disappeared. The nature of the mediastinal mass could not be determined preoperatively. Because of the proximity to the thyroid, it was not possible to determine whether or not the tumor collected I^{131}. The history and clinical picture are best explained by a transient episode of thyrotoxicosis. The I^{131}-test indicated the proper diagnosis.

Case 113 must be classified as a failure of the radioactive iodine tolerance test. It will be discussed together with three other patients in which the radioactive iodine tolerance test gave a misleading result (p. 126).

The twelve remaining patients in this group (Cases 114—125) presented a variety of atypical features (Table 32). The thyrotoxicosis was rather mild in most cases. There was a combination of atypical history and atypical clinical findings. In the history there were few symptoms suggestive of thyrotoxicosis (Cases 116, 117, and 120). Furthermore, the clinical findings were also often equivocal or atypical, with absence of tachycardia (Cases 116—119 and 124) or with negligible increase in thyroid size (Cases 121 and 123). In Case 114 muscle weakness and malaise were outstanding symptoms, and the whole clinical picture was characteristic of what has been called apathetic thyrotoxicosis (LAHEY, 1931). In other patients the thyrotoxicosis was obscured by symptoms such as epigastric pain and back pain (Case 120) or psychoneurotic symptoms (Case 119).

The variety of diagnostic problems in this group of patients may best be illustrated by a few case reports:

Case 122. This 55-year-old woman complained chiefly of swelling of the legs of six days' duration. On arising in the morning she noted that her feet and calves were swollen and that her ankles pitted on pressure. There was a dull aching sensation in the back of her legs. There was nothing in her history to suggest congestive failure. About ten days before admission she noted onset of easy fatiguability, increased sweating, and slight palpitation. She denied nervousness and tremor. It was known that she had had an anemia for which she took iron pills.

The physical examination revealed moderate pitting edema of both calves, a soft thyroid of about 2 × normal size, a pulse rate of 92 –104, and a palpable liver. Otherwise the examination was negative.

The Hgb was 11.0 g. per cent and the RBC was 3,200,000. The NPN was 28 mg. per cent. The blood proteins were 4.97 g. per cent with 3.42 g. per cent albumin and 1.55 g. per cent globulin. The BMR averaged +31 per cent in six tests. PBI's were 12.4 and 10.5 μg. per cent. The 48-hour excretion of I^{131} was 15.1 per cent.

During preoperative treatment with potassium iodide and high protein diet her BMR fell to —4 and —1 per cent and the pulse rate to 70. Her blood proteins rose to 6.50 g. per cent, and her edema disappeared. Thirteen grams of thyroid tissue were removed which showed slight hyperplasia and involution. On examination one year later the BMR was zero and she had gained weight. The Hgb was 15.7 g. per cent (she had taken iron by mouth).

Remarks:—The history did not suggest thyrotoxicosis. The clinical picture was puzzling. She had a small goiter, tachycardia, elevated BMR, edema, low blood proteins, and anemia. The I^{131}-test and the PBI strongly suggested thyrotoxicosis. The response to potassium iodide, the pathological findings, and the subsequent course proved that the diagnosis had been correct.

Case 123. A 71-year-old man was studied because of weight loss and weakness of nine months' duration. Following an attack of a few days of diarrhea with crampy pain he noted progressive weakness and a weight loss of 25 kg. in nine months despite a good appetite. He also suffered from two other episodes of diarrhea for a few days but otherwise his bowel movements were normal. He noticed that he was drinking more water than formerly. He complained of slight dyspnea and palpitation on exertion, slight irritability, and a fine tremor of his hands. There was no nervousness, intolerance to heat, or excessive sweating.

The examination revealed a somewhat emaciated man. There was muscle weakness, a fine tremor of the fingers, and a regular pulse at a rate of 88. The thyroid was of normal size. Barium enema showed a normal colon.

BMR's were +38, +51, and +33 per cent. The 48-hour urinary excretion of I^{131} was 29.4 per cent. *In vivo* measurements demonstrated a high uptake of I^{131} in the thyroid.

During ten weeks' treatment with propylthiouracil the BMR fell to +22 per cent, the pulse rate fell to about 60, and he gained 8 kg. in weight.

Remarks:—This patient represented the oligosymptomatic type of thyrotoxicosis which is not unusual in elderly people. Neither the history nor the clinical findings were characteristic. The clinical diagnosis was difficult, especially in view of the absence of goiter. The I^{131}-test accurately reflected the state of thyroid function.

Case 125. This 44-year-old woman complained chiefly of tiredness of five years' duration. During the past five years she had noted nervousness and crying spells. She had lost 13 kg. in weight but had recently regained about three kg. Her appetite had not been increased. She felt shaky and tremulous and gave a long-standing, complicated psychiatric history with periods of severe depression.

The examination showed a very thin, emotionally unstable woman. There was a fine tremor of the fingers. Thyroid was about 2 × normal size. There were no eye signs. Pulse rate varied between 80 and 130.

BMR's were +28 and +29 per cent. The 48-hour excretion of I^{131} was 30.4 per cent.

During treatment with propylthiouracil and potassium iodide she developed eye signs such as lid retraction and lid lag, and her whole clinical picture became more characteristic of mild thyrotoxicosis. Following a subtotal thyroidectomy her psychiatric symptoms became worse. Further studies could not be carried out.

Remarks:—The history was difficult to evaluate because of the psychiatric problems. When she first was studied the clinical picture was not convincing of thyrotoxicosis, but the low excretion of I^{131} strongly supported the diagnosis, which later became more apparent clinically.

Case 124. A 51-year-old bartender was studied because of a lump in the neck of seven years' duration. It had not changed appreciably in size, nor caused discomfort. He had always been nervous but there was no recent change. He had felt fatigued since having had a severe respiratory infection three months before admission during which he lost four kg. in weight. There was no increased appetite, intolerance to heat, or excessive perspiration. For many years his alcoholic intake had been excessive.

The examination revealed a slightly jaundiced but well-nourished man. There was a slight tremor of the extended fingers. The left lobe of the thyroid consisted of a 8×10 cm. soft mass, which displaced the trachea markedly to the right. The right lobe of the thyroid was easily palpable, perhaps slightly enlarged. X-rays showed a substernal extension. Pulse was regular at a rate of 80. BP was 130/100. The liver was palpable 3—4 cm. below costal margin. The spleen was not felt.

The blood proteins were 7.54 g. per cent with 4.64 g. per cent albumin and 2.90 g. per cent globulin. Urobilinogen in urine was present in a dilution of 1: 500. The cephalin flocculation after 48 hours was + + +. The bromsulfalein test (5 mg./kg.) showed 64 per cent retention after 45 min. BMR's were +29, +25, +28, and +14 per cent. PBI was 11.0 μg. per cent. The 48-hour excretion of I^{131} was 41.8 per cent.

Remarks:—This patient presented a goiter in combination with liver disease. From the history and clinical findings it was not possible to determine whether or not he was thyrotoxic. The slightly elevated BMR might be explained by his chronic alcoholism and liver disease. The excretion of I^{131} suggested thyrotoxicosis as did the PBI. The diagnosis was established by a good response to propylthiouracil.

In this group of 24 patients the 48-hour urinary excretion of I^{131} was less than normal in 23 patients and normal in one patient. The serum protein-bound iodine, determined in 16 patients, was elevated in all but one patient. The results demonstrate that these two tests are valuable aids in the diagnosis of atypical thyrotoxicosis although they are not infallible.

3. Patients in whom thyrotoxicosis was obscured by complicating diseases

Eleven patients (Cases 126—136) were referred to this group (Table 32). Cardiovascular disease was the most common complication and appeared in six patients (Cases 126, 127, 129, 130, 134, and 136). The other coexisting diseases were carcinoma of the lung (Case 133), carcinoma of the rectum (Case 131), Parkinsonism (Case 128),

chronic cholecystitis (Case 135), and masculinizing syndrome (Case 132). Although the BMR was considerably elevated in several patients, it could not be relied upon too heavily for diagnostic purposes, as the complicating disease might have been completely or at least partly responsible for the elevation. For example, Case 129 was observed to have a BMR of +97 per cent when thyrotoxic and +39 per cent in a clinically euthyroid state. In Case 128 the BMR was +60 per cent while thyrotoxic, but still elevated (+34 per cent) when she was completely cured of her disease.

The coexistence of thyrotoxicosis and cardiovascular disease may present diagnostic problems. In the present group of patients the problem of particular importance was to determine whether thyrotoxicosis was present in addition to cardiovascular disease. In Case 129 the diagnosis of thyrotoxicosis could be made clinically, and the decreased excretion of I^{131} was only confirmatory. However, difficult diagnostic problems may arise when organic cardiac disease and thyrotoxicosis are associated, as is illustrated by the following case report:

Case 127. A 47-year-old woman was admitted to the hospital with acute pulmonary edema. Two months prior to admission she began to have "convulsions" of a few minutes' duration. The attacks increased in frequency to about five daily. She was also bothered with vague nervousness, epigastric soreness, and poor appetite. She had lost about four kg. in weight in two months. She claimed that she had had attacks of palpitation for several years, more frequent in the past six months. There was no history of edema or dyspnea on exertion.

The examination (after the acute pulmonary edema had subsided) revealed a soft, nodular thyroid about 2 × normal size. The heart was enlarged particularly in the region of the left ventricle and auricle. There were a systolic and a diastolic murmur on apex and a soft early diastolic murmur to the left of sternum in third interspace. $P_2 + + > A_2$. Pulse was irregular at a rate of 90. BP was 140/80. ECG showed auricular fibrillation at a rate of 110.

Urine contained protein and sugar. Fasting blood sugar was 124 mg. per cent. NPN was 26 mg. per cent. BMR's were +33, +36, +35, and +31 per cent. PBI was 6.9 μg. per cent. The 48-hour excretion of I^{131} was 35.1 per cent, and in a repeated test 34.7 per cent.

She was treated with propylthiouracil and improved considerably. BMR's fell to —5 and +6 per cent. She was later treated with radioactive iodine.

Diagnosis: Rheumatic heart disease (mitral stenosis + mitral insufficiency + aortic insufficiency) + Congestive failure + Thyrotoxicosis.

Remarks:—It was apparent that this patient had organic heart disease, but it was important to determine whether or not she had thyrotoxicosis in addition. From the history and clinical findings it was not possible to make the diagnosis. The BMR's were unreliable because of her cardiac disease. The I^{131}-test indicated thyrotoxicosis, while the PBI was normal. The subsequent course demonstrated that the I^{131}-test had been correct in this complicated case.

Similar diagnostic problems may arise when thyrotoxicosis and hypertensive cardiovascular disease are combined, as is demonstrated by the following patient.

Case 130. This 58-year-old woman complained chiefly of palpitation, shortness of breath, and nervousness of one year's duration. She had had a known but asymptomatic hypertension for 15 years. Rather suddenly, she developed attacks of palpitation. She became dyspneic on one

flight of stairs, noted occasional ankle edema, nervousness, excess sweating, a fine tremor of her hands, and constant fatigue. She had lost 9 kg. in about one year. She had been treated with digitalis but did not improve.

The physical examination showed warm and moist skin, a fine tremor of the extended fingers, and a questionably enlarged thyroid. The fundi showed marked arteriovenous nicking. There was pitting edema of the ankles. The heart was enlarged without characteristic configuration. The pulse rate was 76. There was auricular fibrillation at a rate of 100. BP was 240/125.

There was slight proteinuria and rare red cells in the sediment. The phenolsulfonphthalein excretion was 95 per cent in two hours. BMR's were +23, +23, and +20 per cent. PBI was 9.4 μg. per cent. The 48-hour excretion of I^{131} was 38.1 per cent.

After removal of 30 grams of thyroid tissue the patient improved considerably. When examined about one and a half months later she had gained 5.5 kg. in weight. She felt much stronger, less nervous and less dyspneic, but was still fibrillating. Her BMR had fallen to —1 per cent.

Diagnosis: Thyrotoxicosis (toxic adenoma) + Hypertensive cardiovascular disease.

Remarks:—Clinically it was difficult to determine whether or not thyrotoxicosis was present. The whole clinical picture could be explained on the basis of hypertensive cardiovascular disease. The BMR of +22 per cent was also compatible with hypertension. The fact that the thyroid was not clearly enlarged did not suggest thyrotoxicosis. The I^{131}-test favored the diagnosis of thyrotoxicosis as did the PBI. The subsequent course proved that the diagnosis had been correct.

Similarly, the radioactive iodine tolerance test indicated thyrotoxicosis in Cases 126 and 134. The possibility of pheochromocytoma was raised in Case 136 because of the combination of intermittent paroxysmal hypertension and elevated BMR in a patient in whom neither history nor clinical findings were typical of thyrotoxicosis. The excretion of I^{131} and the PBI were both in the thyrotoxic range.

It may be objected that the low excretion of I^{131} in thyrotoxic patients with cardiovascular disease is due to the latter disease or to renal impairment. However, it will be demonstrated that the urinary excretion of I^{131} is normal in cardiovascular disease not associated with thyrotoxicosis (p. 142).

In Cases 128 and 132 the low excretion of I^{131} confirmed the clinical diagnosis. In spite of a cholecystogram three months previously the radioactive iodine tolerance test suggested thyroid hyperfunction in Case 135. The elevated PBI was without diagnostic significance because of the previous administration of gall bladder dye. The diagnosis of thyrotoxicosis was indicated by the radioactive iodine tolerance test in Case 131, who previously was operated upon for a carcinoma of the rectum and in whom weight loss was the chief complaint. In Case 133, who had carcinoma of the lung, the diagnosis of thyrotoxicosis was borne out by the low excretion of I^{131} and the elevated PBI. The BMR could not be relied upon because of the pulmonary disease.

The results in this group of patients demonstrate that the urinary excretion of I^{131} can be used successfully for the diagnosis of thyrotoxicosis in patients in whom the clinical picture is obscured by a coexisting disease. The test is of particular value when the complicating disease in itself may cause an elevated basal metabolic rate. The serum protein-bound iodine is of similar diagnostic value.

Discussion

It is true that the basal metabolic rate was elevated in this group of 42 patients with thyrotoxicosis. It might then be questioned whether any other laboratory test than the BMR was required for the diagnosis. However, in a large number of the patients the BMR was only slightly elevated. It was below +30 per cent in half of the group. Furthermore, the comparatively low basal metabolic rates occurred in a considerable number of patients in whom the clinical picture was atypical or vague. Greater elevations of the basal metabolic rate occurred particularly in patients in whom an associated disease was partly responsible for the increased BMR.

Under such circumstances there was a definite need for other laboratory tests. The present study has demonstrated that the 48-hour urinary excretion of I^{131} is of great assistance in establishing the diagnosis of thyrotoxicosis in patients in whom the diagnosis cannot be made with reasonable certainty from the clinical picture and the basal metabolic rate. The test is reliable, but it is not infallible. In one of the 42 thyrotoxic patients the radioactive iodine excretion was normal.

Previous investigators (Salter *et al.*, 1941; Riggs, 1947; Winkler, 1947; and others) have demonstrated that the serum protein-bound iodine is a valuable aid in the diagnosis of thyrotoxicosis. The present study has confirmed these earlier observations. The serum protein-bound iodine was determined in 30 patients. There were five patients, however, in whom the PBI could not be used to establish the diagnosis of thyrotoxicosis. In three of these patients the PBI was normal, and in two patients a previous cholecystogram may have been responsible for the elevated PBI. In all these five patients the radioactive iodine tolerance test gave results that supported the diagnosis.

Thyrotoxicosis with Normal Basal Metabolic Rate ($\leq +20$ per cent).

For a long period of time it was considered that thyrotoxicosis with normal basal metabolic rate did not exist or at least was exceedingly rare. There are still investigators who do not accept the diagnosis of thyrotoxicosis if the basal metabolic rate is normal (Simpson, 1948). The review of the literature, however, presented conclusive evidence for the existence of thyrotoxicosis with normal basal metabolic rate.

In regard to the frequency of thyrotoxicosis with normal BMR there are few reports in the literature. Furthermore, the figures differ considerably. Probably the most reliable figures are those of Means (1948) who in 1164 cases of thyrotoxicosis from the Massachusetts General Hospital found that about 12 per cent of the females and 8 per cent of the males had BMR's below +20 per cent. In the present study such patients occurred more frequently (22 per cent), as thyrotoxic patients with

normal BMR's were especially sought out, and a number of patients with unquestioned disease were not studied.

Thirty-nine patients with thyrotoxicosis and normal basal metabolic rates were studied (Cases 137—175). Naturally, most of these patients had BMR's on the plus side, but a few patients had BMR's below zero at the time of study. To facilitate the discussion this group of patients was divided in the same way as was the group with elevated basal metabolic rates.

1. Patients in whom the history and clinical findings were vague but rather suggestive of thyrotoxicosis

Seventeen patients were referred to this group (Cases 137—153). The more important clinical and laboratory data are presented in Table 33.

The thyrotoxicosis in all patients was very mild. The symptoms and signs were suggestive of thyrotoxicosis although they often were too vague to be convincing. In certain patients, for example, Cases 145 and 147, the history was also consistent with anxiety neurosis. Sometimes important symptoms and signs of thyrotoxicosis were missing. When in addition the basal metabolic rate was normal, it was difficult to establish the diagnosis of thyrotoxicosis. Three case reports may best illustrate the clinical picture and the diagnostic problems in this type of patients.

Case 143. This 47-year-old woman was studied because of a lump in her left neck which she had noticed for one year. It did not cause any local symptoms nor did it increase in size. She had lost nine kg. in weight in one year and a half on an intentional reduction diet. She had noted slight palpitation on exertion, a fine tremor of her hands, and somewhat increased nervousness. There was no increased perspiration, heat intolerance, or weakness.

The physical examination was negative except for fine tremor of the hands, a 3×4 cm. firm, nontender, movable nodule in the left lobe, and a slightly enlarged right lobe of the thyroid. Pulse was regular at a rate of 90.

BMR's were +13, +18, +17, and +24 per cent. PBI was 11.1 μg. per cent. The 48-hour excretion of I^{131} was 36.8 per cent.

Nineteen grams of thyroid tissue were removed. The nodule in the left lobe was found to be a fetal adenoma. The surrounding thyroid tissue was quite firm and meaty and had the appearance of involuted hyperplastic thyroid tissue. It was not characteristic of the atrophic tissue adjacent to a hyperfunctioning adenoma. The right lobe contained several small nodules, one of which was found to be a papillary adenocarcinoma of low grade malignancy. On examination one year later the patient felt well. She had gained weight. Her BMR was +6 per cent. Pulse rate was 72. There was no evidence of recurrent tissue in the neck.

Remarks:—The diagnosis of thyrotoxicosis was not apparent clinically. The possibility of toxic adenoma was raised because of the nodule in the left lobe. The I^{131}-test and the PBI indicated thyroid hyperfunction. The diagnosis of toxic adenoma was excluded by *in situ* measurements which demonstrated that the large nodule in the left lobe collected less I^{131} than did the right lobe. This observation

was confirmed postoperatively from analyses of I^{131} in the nodule and in the rest of the gland.

The carcinoma was an incidental finding as it usually is in the rare instances when thyrotoxicosis and carcinoma are associated (Pemberton and Black, 1948).

Case 148. A 66-year-old woman complained chiefly of a lump in her neck which she had noticed for one month. The lump did not cause any pressure symptoms. She had lost about nine kg. in weight in three years. Her appetite was good but not particularly increased. For many years she had disliked hot weather, had been somewhat nervous, had noted a slight tremor of her hands and palpitation of her heart when she became excited.

The examination revealed a slightly overactive woman. The skin was warm but not moist. There was a fine tremor of the extended fingers. The thyroid showed a 3×3 cm. smooth, firm nodule in the right lobe. The isthmus was palpable. The left lobe was not definitely palpable. The trachea was slightly displaced to the left. Pulse was regular at a rate of 88. BP was 155/80.

BMR's were +17, +15, and +15 per cent. PBI was 12.0 μg. per cent. The 48-hour excretion of I^{131} was 34.5 per cent.

She was prepared for surgery with potassium iodide and a right hemithyroidectomy was performed. The removed tissue consisted primarily of an encapsulated adenoma which on microscopic examination showed signs of hyperplasia and involution. On examination one and a half months later she had gained 2.5 kg. in weight and felt markedly improved. Her BMR was —12 per cent.

Remarks:—The diagnosis of thyrotoxicosis was not conclusive from her history and clinical findings. The I^{131}-test was in keeping with the diagnosis of thyrotoxicosis as was the PBI. *In situ* measurements over the thyroid demonstrated that practically all the I^{131} was located in the large nodule in the right lobe, thus proving that this was a hyperfunctioning adenoma. The response to treatment established that she had had thyrotoxicosis.

Case 150. This 32-year-old woman complained chiefly of constant nervousness which had become worse three weeks prior to entry. She had always been irritable and emotionally unstable. She was bothered by dyspnea and palpitation on exertion. Two years before admission she received X-ray treatment over her thyroid and improved considerably. Her symptoms returned during a pregnancy, terminated six months prior to admission. Despite increased appetite she lost five kg. in weight. Her nervousness increased, she cried easily and felt weak. She had no intolerance to heat, nor did she perspire excessively. A sister had recently had thyrotoxicosis.

The examination showed an extremely overactive and emotionally labile woman. The skin was warm and moist. There was no tremor. The thyroid was about $1\ ^1/_2 \times$ normal size. It was smooth and soft. There were lid lag, globe lag, stare, and difficulty in convergence, but no exophthalmos. Pulse was regular at a rate of 104. BP was 115/80.

BMR averaged +19 per cent in six tests. PBI's were 6.5 and 5.8 μg. per cent. The 48-hour excretion of I^{131} was 16.5 per cent.

After three months' treatment with potassium iodide her BMR was —13 per cent, and she had gained three kg. in weight. PBI was 5.8 μg. per cent. The thyroid gland had become definitely firmer. Therapy was discontinued. One month later her BMR was +23 per cent and PBI was 10.0 μg. per cent. When potassium iodide was reinstated, the BMR fell to —10 per cent.

Remarks:—Although the history and clinical findings were consistent with thyrotoxicosis they could also be explained on the basis of a long-standing anxiety state.

Clinically the diagnosis was far from clear-cut. The BMR was normal as was the PBI. The I^{131}-test indicated thyrotoxicosis. The subsequent course demonstrated that the latter test had been correct.

This case shows that the excretion of I^{131} may become low before PBI becomes elevated. It is probable that the thyroid's increased avidity for iodine often appears earlier than does the elevation of the PBI. However, it is only in exceptional cases that studies can be made during this phase of the development of thyrotoxicosis.

The 48-hour urinary excretion of I^{131} indicated thyrotoxicosis in 14 patients but failed to do so in three patients (Cases 151, 152, and 153). In Case 151 the excretion was 44.9 per cent and thus very near the lower normal 3σ limit (44.0 per cent). These three patients with normal excretion of I^{131} will be discussed separately (p. 126).

The serum protein-bound iodine, determined in 14 patients, was elevated in 12 cases. In the two patients with normal values (Cases 139 and 150) the radioactive iodine tolerance test suggested thyrotoxicosis. In Case 150 the PBI became elevated when this patient developed frank hyperthyroidism a few months later.

The results indicate that the radioactive iodine tolerance test may be used in establishing the diagnosis in clinically mild thyrotoxicosis when the basal metabolic rate is normal. The test is not entirely reliable, however. The serum protein-bound iodine was of similar diagnostic value in this group. It should be observed that there were no patients in whom both the radioactive iodine tolerance test and the serum protein-bound iodine were normal simultaneously.

2. Patients in whom the history and/or the clinical findings were not characteristic of thyrotoxicosis

Seventeen patients were referred to this group (Cases 154—170). The clinical and laboratory data are presented in Table 33.

These patients presented a variety of diagnostic problems. The paucity of typical symptoms in the history was the main concern in Cases 154, 155, and 156 in whom the clinical picture was suggestive of thyrotoxicosis. Rather characteristic histories were observed in Cases 157—161, but the clinical findings were unimpressive (Cases 157 and 161) or atypical with almost exclusively cardiovascular symptoms (Cases 159 and 160) or lack of goiter (Cases 158, 159, and 160). The diagnostic problems may be illustrated by the following case report:

Case 160. A 76-year-old man complained chiefly of dyspnea and palpitation of six years' duration. He was told by a doctor that he had emphysema and was given a cough medicine that contained potassium iodide. On this medication he noted that his pulse became slower, and he felt better. One year before admission he omitted his cough medicine and soon thereafter his previous symptoms became worse. His appetite became poor and he lost 17 kg. in weight. He felt fatigued. He noted no intolerance to heat, sweating, or nervousness. Two months before admission his family doctor started him on Lugol's solution and digitalis, on which treatment his condition improved.

The examination showed an emaciated, slightly hyperactive man. The skin was warm but dry. There was no tremor. The thyroid was not enlarged. X-rays showed no substernal extension. There were slight stare and lid retraction but no exophthalmos. He was orthopneic. X-rays of the chest showed emphysema and fibrosis with bleb formation. Pulse was regular at a rate of 80. BP was 140/90. ECG was consistent with coronary disease and intraventricular block.

BMR was —6 per cent. The 48-hour excretion of I^{131} was 17.8 per cent seven days after discontinuing Lugol's solution. The patient was studied again three weeks later, having had no medication in the interval. BMR's were then +19, +39, and +19 per cent. PBI was 8.6 μg. per cent and the 48-hour excretion of I^{131} was 14.5 per cent.

He was treated with 10 mc. of I^{131}. He responded well. On examination three months later he had gained 6 kg. in weight. The BMR had fallen to —26 per cent, but there were no symptoms of hypothyroidism.

Remarks:—This patient presented a history and a clinical picture that are not unusual for thyrotoxicosis in elderly people. The cardiovascular symptoms were predominant. The thyroid was not enlarged. The reported response to iodine made thyrotoxicosis likely. From the physical examination a diagnosis of thyrotoxicosis could not be made. Two interesting points should be mentioned. The I^{131}-test indicated thyrotoxicosis as early as seven days after discontinuation of iodine therapy. The increased avidity for I^{131} was demonstrated when the BMR was —6 per cent.

The remaining nine patients (Cases 162—170) presented a variety of atypical features in both the history and clinical findings as is indicated in Table 33. In some patients there was no loss of weight (Cases 162, 164, 167, and 168) but even gain in weight (Cases 163 and 166). There were such symptoms as constipation (Cases 162 and 163). Epigastric pain, weight loss, and anorexia were the chief symptoms in Case 170. The clinical picture was not characteristic as several important signs were missing. For example, there was sometimes no goiter (Cases 163, 164, 167, and 168), the skin was normal (Cases 162, 167, 169, and 170), there was no tremor (Cases 162, 163, 165, and 170) or no tachycardia (Cases 165, 168, and 169).

The unusual features and the diagnostic problems may be illustrated by a few case reports:

Case 162. This 57-year-old woman complained chiefly of nervousness and lack of initiative. She had been nervous and over-emotional all her life. For many years she had had gaseous indigestion, constipation, and slight palpitation. About ten years before admission she first noted a lump in her neck. Six years before admission she was seen in the medical out-patient department complaining of nervousness, palpitation, and fatigue. BMR's were +13 and +24 per cent. She was given potassium iodide as a therapeutic trial but no response was observed. She was then treated for a psychoneurosis but her symptoms remained unchanged. She continued to feel nervous and fatigued.

The examination revealed a jittery and talkative woman. The thyroid was about 3 × normal size with a 3 × 3 cm. nodule in the isthmus. The whole gland was somewhat irregular and moderately firm. Pulse was regular at a rate of 84.

BMR's were +12 and +11 per cent. PBI was 9.5 μg. per cent. A PBI taken four months earlier had been 9.2 μg. per cent. The 48-hour excretion of I^{131} was 37.5 per cent.

During the preoperative treatment with potassium iodide, the BMR did not change but the

Table 33. **Clinical and laboratory data in thyrotoxic pati**

Case number	Age Sex	History										Physical examination									
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes			Heart		Pulse rate	Blood pressure
															Exophthalmos	Lid lag	Lid retraction	Enlargement	Fibrillation		
137	48 ♀	+	+	0	0	+	0	0	0	+	+	2, D, f	w, m	+	+	+	+	0	0	100	170/100
138	21 ♀	+	+	0	0	+	+	0	0	+	0	1½–2, D, f	n	+	0	0	0	0	0	108	
139	40 ♀	0	0	+	0	+	+	+	+	+	0	1½, N, f	w, m	+	0	0	+	0	0	84	150/80
140	63 ♂	0	+	0	+	0	0	+	0	+	+	2–3, N, s	w, m	+	0	0	0	0	0	80	155/90
141	59 ♀	+	+	+	+	+	0	+	0	+	+	2–3, D, f	w, m	+	0	0	+	0	0	90	170/85
142	69 ♂	+	0	0	0	0	0	0	+	+	+	1½, D, s	n	+	+	0	0	+	0	80	135/85
143	47 ♀	+	0	0	0	0	+	+	0	+	+	1½, N, f	n	+	0	0	0	0	0	90	130/80
144	67 ♀	+	+	+	0	+	0	+	+	0	+	5, N, f	n	+	0	+	0	0	0	104	165/90
145	43 ♂	+	0	0	0	+	0	0	0	+	+	1½, D, s	w	+	0	+	0	0	0	96	130/80
146	32 ♀	0	+	+	+	0	0	0	+	0	0	1½–2, D, f	w, m	+	+	0	+	0	0	126	120/70
147	30 ♀	–	+	+	+	+	+	0	0	+	+	1½–2, D, s	w, m	+	0	+	+	0	0	90	110/70
148	66 ♀	+	0	+	+	0	+	+	0	+	+	1½, N, f	w	+	0	0	0	0	0	88	155/80
149	29 ♀	+	+	+	+	+	+	0	0	0	+	1½, D, f	m	0	0	0	0	0	0	116	115/60
150	32 ♀	+	+	+	+	+	+	+	0	+	+	1½, D, s	w, m	0	0	+	+	0	0	104	115/80
151	65 ♀	0	0	+	0	+	+	+	0	+	0	2–3, N, f	w, d	0	0	0	0	0	0	120	180/80
152	57 ♂	+	+	+	+	+	0	0	0	+	+	2, N, s	n	+	0	+	+	0	+	90	125/70
153	38 ♀	0	+	0	0	+	+	0	+	0	+	2–2½, D, f	n	+	+	+	+	0	0	86	115/85
154	55 ♀	+	0	0	0	0	0	0	0	0	+	1½, D, s	w, m	+	0	0	0	0	0	100	150/80
155	28 ♀	0	0	0	0	+	+	0	+	+	0	2, D, f	w, d	+	+	0	+	0	0	96	130/70
156	28 ♀	0	0	0	0	+	0	+	+	+	0	2, D, s	w, m	+	+	+	0	0	0	80	
157	25 ♀	+	+	+	+	+	+	0	0	+	0	1½–2, D, s	w, d	+	0	0	+	0	0	92	130/75
158	54 ♂	+	0	+	+	+	+	0	0	+	+	1, D, f	w, d	+	0	+	+	0	0	90	155/80
159	59 ♀	+	0	+	0	+	+	0	0	+	0	1–1½, N, f	w, d	0	0	0	0	0	+	76	145/75
160	76 ♂	+	0	0	0	+	+	0	0	0	0	1, D, f	w, d	0	0	+	+	0	0	80	140/90
161	27 ♀	+	0	0	+	+	+	+	0	+	0	1½, N, f	w	0	0	0	0	0	0	86	110/65
162	57 ♀	0	0	0	0	+	+	+	0	+	0	3½, N, f	n	0	0	0	0	0	0	84	140/80
163	52 ♀	0	0	+	+	+	+	0	0	+	0	1, D, f	w, m	0	0	0	0	0	0	95	135/65
164	65 ♀	0	0	+	+	+	0	+	0	+	+	1, N, f	m	+	0	+	+	0	0	94	150/70
165	26 ♀	+	0	0	0	+	+	0	0	+	0	2, D, f	w	0	0	+	+	0	0	74	130/50
166	55 ♀	0	0	0	0	0	+	+	0	+	+	1½, N, f	w	+	0	0	0	0	0	84	140/70
167	33 ♀	0	0	0	0	+	+	0	0	+	+	1, D, s	n	+	0	0	0	0	0	110	110/70
168	39 ♀	0	0	0	+	0	+	0	0	+	0	1, D, f	w, d	+	0	0	0	0	0	80	

normal BMR and presenting diagnostic problems.

Laboratory findings					Complicating disease	Treatment	Result of treatment	Remarks
BMR per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent: 0—24 hours	24—48 hours	Total in 48 hours				
+19		21.7	3.3	25.0		I^{131}	+	
+17	7.7	34.2	3.1	37.3		KI	+	Recurrent thyrotoxicosis.
+15	5.3	38.1	1.3	39.4		op.	+	Recurrent thyrotoxicosis.
+ 5		31.5	4.8	36.3		op.	+	I. v. pyelogram 4 days before I^{131}-test.
+19	9.5	32.2	1.2	33.4		I^{131}	+	
— 2	7.8	12.3	0.9	13.2	Myocardial infarction	I^{130}	+	TU for 2 months. Discontinued 6 days prior to study.
+18	11.1	33.5	3.3	36.8	Carcinoma of the thyroid	op.	+	
+ 1	13.0	18.9	3.5	22.4	Duodenal ulcer	op.	+	KI discontinued 10 days prior to study.
+20		18.4	1.1	19.5		op.	+	
+ 3	9.6	30.5	1.0	31.5		KI	+	
+ 6	8.6	37.3	2.1	39.4	Psychoneurosis	KI	+	
+16	12.0	29.7	4.8	34.5		op.	+	Toxic adenoma.
+12	10.1	39.8	1.5	41.3		op.	+	
+19	6.2	13.8	2.7	16.5		KI	+	
+ 7	8.3	38.2	6.7	44.9		I^{131}	+	
+ 8	8.8	52.9	2.9	55.8		I^{131}	+	
+14	10.1	56.2	2.5	58.7		I^{131}	+	
+20		21.1	0.4	21.5		I^{131}	+	Recurrent thyrotoxicosis.
+18		23.4	1.2	24.6		I^{131}	+	Recurrent thyrotoxicosis.
+13	10.4	25.4	5.2	30.6		KI	+	
+11	7.5	35.7	0.0	35.7		KI	+	
+20		28.0	2.4	30.4		op.	+	
+ 8	9.8	35.5	1.1	36.6	Congestive failure	I^{131}	+	Recurrent thyrotoxicosis.
— 6	8.6	16.8	1.0	17.8	Emphysema + Arteriosclerosis	I^{131}	+	Lugol's solution discontinued 7 days before I^{131}-test.
— 4		27.7	1.6	29.3		op.	+	
+12	9.5	36.7	0.8	37.5	Psychoneurosis	op.	+	
+18	13.3	23.4	1.4	24.8		I^{131}	+	Recurrent thyrotoxicosis.
— 3		33.8	1.4	35.2		op.	+	Toxic adenoma.
+16	4.7	12.2	1.0	13.2	Epilepsy	op.	+	I^{131}-test 3 weeks later than BMR and PBI.
+11	9.5	22.1	0.9	23.0		op.	+	Toxic adenoma.
+17	10.7	21.8	0.8	22.6		op.	+	
+11	9.7	32.2	1.2	33.4		0	+	Spontaneous remission.

(Cont.).

Case number	Age Sex	History										Physical examination									
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes			Heart		Pulse rate	Blood pressure
															Exophthalmos	Lid lag	Lid retraction	Enlargement	Fibrillation		
169	51 ♀	+	0	0	0	0	+	+	0	+	0	1½, N, f	n	+	0	0	0	0	0	70	120/80
170	48 ♂	+	0	0	0	+	0	0	0	0	0	2, D, f	n	0	0	+	+	0	0	100	120/55
171	50 ♀	0	0	0	0	+	+	0	+	+	0	2–3, N, f	w, m	0	0	+	+	+	0	88	120/90
172	44 ♀	+	+	+	+	+	+	0	0	+	+	2, D, f	w, m	0	0	+	0	0	0	80	130/70
173	21 ♀	+	+	+	+	+	+	0	0	+	+	2, D, f	w, m	0	0	0	0	0	0	90	110/60
174	23 ♂	+	0	0	0	+	0	0	0	+	0	1, N, f	w, m	+	0	0	0	0	0	85	140/100
175	57 ♀	+	0	0	0	+	0	0	0	+	0	1½–2, N, f	n	+	0	0	0	+	0	90	140/100

gland became definitely firmer. Ninety-one grams of thyroid tissue were removed. The pathological diagnosis was that of toxic nodular goiter. On examination six months later she had gained seven kg. in weight, her pulse rate had fallen to 58 and her BMR to —15 per cent. There were no symptoms of hypothyroidism. Her psychoneurotic symptoms were substantially unchanged.

Remarks:—The differential diagnosis was extremely difficult. There obviously had been a long-standing psychoneurosis. If there were thyrotoxicosis in addition, treatment of the latter disease might benefit her psychoneurosis. The diagnosis of thyrotoxicosis could not be made clinically. The PBI and the I^{131}-excretion were suggestive of thyrotoxicosis. The findings of a hyperplastic gland and the subsequent course established the diagnosis of mild thyrotoxicosis.

Case 165. A 26-year-old woman complained chiefly of weight loss of six months' duration. Since the birth of her first child four years previously she had been extremely nervous and irritable and had had occasional epileptiform seizures. There was a recent weight loss of nine kg. There had been no recent change in her usually excellent appetite and preference for warm weather. She had been troubled by rapid beating of her heart, dyspnea on exertion, and weakness.

The examination revealed a somewhat overactive and restless woman. The skin was warm but not abnormally moist. There was no tremor of the fingers. Her thyroid was diffusely en-

Laboratory findings					Complicating disease	Treatment	Result of treatment	Remarks
BMR per cent	PBI μg per cent	Urinary excretion of I^{131} in per cent: 0—24 hours	24—48 hours	Total in 48 hours				
+ 7	10.9	30.2	1.4	31.6		op.	+	
+19	16.6	64.4	11.6	75.0		op.	+	Cholecystogram 23 days prior to study.
+16		9.6	0.3	9.9	Rheumatic heart disease + Congestive failure + Active rheumatic infection	I^{130}	+	
— 4	4.8	19.8	7.9	27.7	Bronchial asthma	I^{131}	+	Recurrent thyrotoxicosis. KI discontinued 7 days prior to I^{131}-test.
+19		12.0	0.8	12.8	? Addison's disease	op.	+	
+16	8.7	22.6	1.4	24.0	Psychoneurosis ? Schizophrenia	I^{131}	+	Recurrent thyrotoxicosis.
+12	8.4	31.9	7.7	39.6	Coronary and rheumatic heart disease + Congestive failure + Diabetes mellitus.	TU	+	Died from myocardial infarction.

larged to about 2 × normal size, and of rubbery consistency. There were lid lag, globe lag, and impairment of convergence, but no exophthalmos. The pulse was regular at a rate of 74. BP was 130/50.

BMR was +16 per cent. PBI was 4.7 μg. per cent. The 48-hour excretion of I^{131} was 13.2 per cent three weeks later. In another month she had developed characteristic thyrotoxicosis. The BMR rose to +42 per cent and the PBI to 15.2 μg. per cent. Following thyroidectomy all her toxic symptoms disappeared. On examination nine months later she had gained four kg. in weight, felt fairly well, but showed certain symptoms of hypothyroidism with a BMR of —27 per cent.

Remarks:—The diagnostic problem in this patient was resolved by the development of frank hyperthyroidism. The I^{131}-test indicated thyrotoxicosis earlier than did the clinical picture.

Case 166. A 55-year-old woman complained chiefly of palpitation of the heart of about two years' duration. She had had a goiter for 20 years, which had not increased in size. In the seven years before admission she had lost about 20 kg. in weight but had regained about 10 kg. during the previous year and a half. Her appetite had always been good and never particularly increased. She had also noticed increased nervousness, irritability, and tremor of her hands. She disliked cold weather, became very flushed in hot weather, but did not perspire excessively. During the two years before admission she noted dyspnea and palpitation on slight exertion or with excitement. For several years she had had swelling of her ankles.

The examination showed a somewhat overactive woman. There was a fine tremor of the extremities. The skin was warm but not very moist. The thyroid had a 4×3 cm. firm nodule in the right lobe displacing the trachea to the left. The left lobe was of normal size. There was slight ankle edema. The heart was at the upper limit of normal. Pulse was regular at a rate of 84. BP was 140/70.

BMR's varied between +6 and +17 per cent in five tests. PBI's were 9.8 and 9.2 μg. per cent. The 48-hour excretion of I^{131} was 23.0 per cent.

Twenty-six grams of thyroid tissue were removed which consisted mainly of an adenoma. Postoperatively she developed auricular flutter with fibrillation at times, but she was restored to normal rhythm with quinidine. On examination one month later she had improved markedly. Her pulse had fallen to 60 and was regular. BMR was —19 per cent.

Remarks: —The history and clinical picture suggested that the cardiac symptoms in this patient were due to mild thyrotoxicosis from a hyperfunctioning adenoma. Several of the classic symptoms were missing, however. The fact that she had gained about 10 kg. in weight during the past year and a half as well as her intolerance to cold weather made the clinical diagnosis uncertain. The I^{131}-test and the PBI indicated thyroid hyperfunction. The subsequent course proved that both tests had been correct.

Case 167. A 33-year-old woman complained chiefly of fatigue of three to four months' duration. Some months earlier she had lost three kg. in weight which she had regained, however. She had felt nauseated and had vomited occasionally. Her bowel movements had become somewhat more frequent. She was bothered by palpitation and dyspnea on exertion. She had felt nervous and irritable but had lived under great emotional tension.

The examination showed a thin, tense woman. There was a minimal tremor of the extended fingers. The thyroid was barely palpable. The left eye looked more prominent than the right, but exophthalmometer measurements did not reveal any difference. There were levator spasm, pronounced globe lag, and periorbital edema of the left eye. Pulse was regular at a rate of 110. BP was 110/70.

BMR's were +18, +24, and +9 per cent. PBI was 10.7 μg. per cent. The 48-hour excretion of I^{131} was 22.6 per cent.

The patient did not return until one year later. She had received no treatment in the meantime. On her return the diagnosis of thyrotoxicosis was clear-cut clinically. The BMR was +29 per cent. The PBI was 15.0 μg. per cent. The 48-hour excretion of I^{131} was 18.1 per cent. At operation sixteen grams of thyroid tissue were removed. On the microscopic examination of the thyroid, groups of epitheloid cells consistent with sarcoid lesions were found.

Two months later she had gained 4 kg. and felt well. BMR was —21 per cent.

Remarks:—On the first examination the history and clinical findings were consistent with early mild thyrotoxicosis. The I^{131}-test and the PBI indicated thyroid hyperfunction in spite of the normal size of the gland. Hyperthyroidism in the presence of demonstrable sarcoid lesions in the thyroid gland has been described previously (Oldberg, 1943). The causal relation is obscure.

In this group the urinary excretion of I^{131} was decreased in 16 patients and normal in one patient. However, the normal value, obtained in Case 170, did not give any information about the functional state of the thyroid because of a cholecystogram only 23 days previously.

The serum protein-bound iodine, determined in 12 patients, was elevated in ten patients but was normal in Case 157. In Case 165 the PBI first was normal but became elevated a few weeks later. The elevated PBI in Case 170 could not be used as an argument favoring thyrotoxicosis because of the previous administration of gall bladder dye.

There is no doubt that this group of patients presented diagnostic problems. It was not possible to establish the diagnosis from the clinical picture at the time of study. The basal metabolic rate was normal and was thus of no aid. Under such circumstances the radioactive iodine tolerance test added strong support for the diagnosis.

3. Patients in whom thyrotoxicosis was obscured by complicating diseases

Five patients (Cases 171 175) were referred to this group (Table 33). The complications were cardiac disease (Cases 171 and 175), bronchial asthma (Case 172), severe psychoneurosis (Case 174), and possibly Addison's disease (Case 173). In Cases 175 and 171 the problem was to determine whether thyrotoxicosis was present in addition to cardiac disease with congestive failure. Case 175 may serve to exemplify the diagnostic problems in such patients.

Case 175. This 57-year-old woman complained chiefly of shortness of breath of six months' duration. She had had diabetes mellitus for at least 11 years. Her diabetes was fairly well controlled by 35 units of protamine zinc insulin daily. Five weeks before admission she had observed a marked increase in her symptoms. She became constantly short of breath and had many attacks of nocturnal dyspnea. She also noticed that her abdomen became swollen as did her legs. She had lost 10 kg. in weight in six months despite a fairly good appetite.

The examination showed an obese, markedly dyspneic woman. The thyroid was about $1\ ^1/_2$—$2\times$ normal size. It was nodular and moderately firm. There were no eye signs. The heart was generally enlarged. There was a protodiastolic gallop rhythm along the left sternal border. Both systolic and diastolic murmurs were heard over the apex. Pulse was regular at a rate of 90. BP was 140/100. ECG showed slight intraventricular block. The liver was palpable seven cm. below the costal margin. There was pronounced pitting edema of the legs.

Urine showed positive tests for protein and sugar. NPN was 32 mg. per cent. Fasting blood sugar was 285 mg. per cent. BMR's were +11, +9, +12, and +14 per cent. PBI's were 9.7 and 7.1 μg. per cent. The 48-hour excretion of I^{131} was 39.6 per cent.

She was treated with insulin, digitalis, diuretics, thiouracil, and iodine, and improved considerably. During treatment with thiouracil and iodine her pulse rate fell, while digitalis alone had failed to lower the pulse rate. Her edema disappeared. BMR's fell to about zero. Her diabetes improved, and she required less insulin. About three months later the patient died suddenly from a myocardial infarction.

Diagnosis: Coronary heart disease with myocardial infarction − Rheumatic heart disease with aortic and mitral involvement + Diabetes mellitus + Thyrotoxicosis.

Remarks:—This patient presented a diagnostic problem in respect to her thyroid condition. Clinically it was not possible to evaluate her thyroid status. BMR's

were not too dependable under the existing conditions. The I^{131} -test was suggestive of hyperthyroidism as was the PBI. After the definite response to treatment it was the consensus of opinion that this patient had mild thyrotoxicosis. Because of the treatment with thiouracil it was not possible to determine at autopsy whether the hyperplasia of the thyroid was due to thyrotoxicosis or to thiouracil treatment.

Case 171 was previously treated with thiouracil, but this had been discontinued. The problem was to determine whether thyrotoxicosis was still present.

In Case 174 there was no doubt that the patient had some psychiatric disease (severe psychoneurosis or possibly schizophrenia). Whether or not thyrotoxicosis was present in addition could not be settled clinically. The urinary excretion of I^{131} and the PBI both indicated thyrotoxicosis which proved to be correct by the subsequent course.

In Case 172 the clinical picture of thyrotoxicosis was obscured by the presence of bronchial asthma. In spite of previous treatment with potassium iodide (discontinued one week prior to study) the I^{131}-test demonstrated thyroid hyperfunction. Simultaneously, the PBI and the BMR were normal. Ten days later the PBI was elevated while the BMR was still normal. The results show that in this patient the escape from the previous iodine medication was reflected earlier in the I^{131}-test than in the PBI.

The finding of a normal basal metabolic rate in patients who had thyrotoxicosis in association with cardiac disease and congestive failure is rather surprising. One would have expected that two diseases which both tend to increase the BMR would have raised the BMR above normal. Even with the combination of thyrotoxicosis and bronchial asthma the finding of a normal BMR was unexpected.

The urinary excretion of I^{131} was less than normal in all five patients. This shows that the test is a helpful diagnostic tool even in most complicated patients with thyrotoxicosis.

Patients in whom the Radioactive Iodine Tolerance Test Failed to Indicate Thyrotoxicosis

In four patients with thyrotoxicosis (Cases 113, 151, 152, and 153) the radioactive iodine tolerance test gave misleading results. The clinical and laboratory data are presented in Table 32 (Case 113) and Table 33 (Cases 151, 152, and 153).

It is not entirely clear that the test should be considered a failure in all four patients. However, the PBI did indicate thyrotoxicosis in these patients. The BMR was normal in three of the patients.

In Case 113 the diagnosis of thyrotoxicosis was not absolutely certain although a mild thyrotoxicosis was most likely. The BMR and the PBI were elevated. However, the postoperative course was not characteristic of thyrotoxicosis. Her symptoms showed no marked change, the pulse rate did not drop, but the BMR became normal.

The normal excretion of I^{131} was not explained. She had taken a number of drugs previously, but it was never proved that they contained iodine. She also had had previous X-ray examinations of her abdomen, but it could not be ascertained that gall bladder dye was administered.

Case 152 presented a clinical picture that was suggestive of thyrotoxicosis, but the diagnosis could not be definitely established clinically. The BMR was +8 per cent. The PBI was elevated, but the urinary excretion of I^{131} was normal. This patient later developed apparent clinical thyrotoxicosis. The failure of the radioactive iodine tolerance test to indicate thyrotoxicosis might have been due to a spontaneous remission a short time before the present study. This is supported by the fact that two months previously the BMR was +22 per cent. Furthermore, when potassium iodide was administered the response was more rapid than usual. However, it seems most correct to classify this case a failure of the radioactive iodine tolerance test.

Case 153 presented a history and a clinical picture of early mild thyrotoxicosis. She also had a detached retina. The BMR was normal, but the PBI was elevated. The urinary excretion of I^{131} was normal (58.7 per cent). She was treated with potassium iodide for eight months. Ten days after discontinuation of therapy the urinary excretion of I^{131} was 22.8 per cent. There was no explanation found for the normal excretion of I^{131} on the first occasion. In this case the PBI indicated thyrotoxicosis earlier than did the radioactive iodine tolerance test.

The last patient, Case 151, had a mild thyrotoxicosis. The BMR was normal, and the PBI was elevated. The 48-hour urinary excretion of I^{131} was 44.9 per cent. The lower 3σ limit for the normal is 44.0 per cent. The value, then, was almost outside the normal range.

The most reasonable explanation for the failures is probably that these patients when euthyroid had a high normal excretion of I^{131}. When thyrotoxicosis developed the thyroid's avidity for iodine did not increase enough to bring the urinary excretion of I^{131} below normal. It is also possible that previous iodine administration in one form or another had contributed to produce the comparatively high excretion of I^{131}. A previous thyroid medication would also give the same effect. However, no history of excessive intake of iodine or thyroid could be elicited.

The present study has demonstrated that there is only a small number of thyrotoxic patients in whom the radioactive iodine tolerance test fails to detect thyrotoxicosis. The failures are too rare to detract appreciably from the diagnostic value of the test.

Discussion

This group of patients with thyrotoxicosis and normal basal metabolic rates consisted of 39 cases. Because of the normal basal metabolic rate it can be said at once that all these patients represented diagnostic problems. The types of diagnostic

Table 34. **Clinical and laboratory data in patients in w**

Case number	Age Sex	History										Physical examination									
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes			Heart		Pulse rate	Blood pressure
															Exophthalmos	Lid lag	Lid retraction	Enlargement	Fibrillation		
183	55 ♂	0	0	+	0	0	0	0	+	+	0	1½, D, f	w, m	+	+	+	+	0	0	76	
184	32 ♀	+	+	+	+	+	0	+	+	+	+	1½, D, f	w	+	+	+	+	0	0	100	120/80
185	52 ♀	0	0	0	0	+	0	0	0	+	0	1½, D, s	n	0	+	0	0	0	0	84	120/80
186	72 ♀	+	0	0	+	+	+	0	0	+	+	1, D, f	w, m	+	0	0	0	0	0	104	135/65
187	54 ♀	+	0	+	0	+	0	0	0	+	0	1½—2, N, f	n	0	0	0	0	+	+	80	200/100

problems varied a great deal as the previous discussion has indicated. In about half of the patients the symptoms and signs of thyrotoxicosis were rather characteristic, but the whole clinical picture was too vague and undifferentiated to permit a clinical diagnosis. The second type of problem arose in patients with an atypical clinical picture. Sometimes there were very few characteristic symptoms and signs. In other cases the thyrotoxicosis manifested itself in an unusual fashion. The third type of problem was presented by patients in whom thyrotoxicosis was associated with a nonthyroid disease. There is no doubt that even the most capable clinician needs additional laboratory tests when dealing with such patients. The basal metabolic rate, of course, was on the plus side in most patients. In a number of patients, however, the BMR was less than zero. Apparently these very low BMR's occurred in patients whose BMR in a euthyroid state was still much lower, sometimes below the accepted normal limit. In these patients the basal metabolic rate fell to —15 to —20 per cent or even lower when they were rid of their thyrotoxicosis, but they did not develop symptoms of hypothyroidism.

Two types of rather characteristic clinical pictures merit further comment from the diagnostic point of view. The first type is represented by those patients in whom the thyrotoxicosis appears in the guise of a psychoneurosis. In such patients the thyrotoxicosis may be easily overlooked, particularly if the BMR is normal. The second type is represented by those patients in whom cardiovascular symptoms dominate the clinical picture. It may be that the cardiovascular symptoms are thyrotoxic manifestations or that thyrotoxicosis appears in addition to an organic cardiovascular disease. In both categories it may be difficult or impossible to establish the diagnosis from the clinical picture and the basal metabolic rate.

The present study has demonstrated that the radioactive iodine tolerance test offers a rather reliable and sensitive method for the diagnosis of thyrotoxicosis even

toxicosis was suspected but not definitely proved or disproved.

Laboratory findings					Complicating disease	Treatment	Result of treatment	Remarks
BMR per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent						
		0—24 hours	24—48 hours	Total in 48 hours				
+19		18.9	1.5	20.4		KSCN	+	
+ 4	4.8	30.1	0.7	30.8		KI	+	
+ 2	7.7	40.7	1.6	42.3		KI	+	
+ 4		13.8	3.3	17.1	Nephrosclerosis	I^{131}	?	? Recurrent thyrotoxicosis.
+12	(12.1)	59.3	1.5	60.8	Rheumatic heart disease	I^{131}	0	

in the most problematic cases. In the present material of 39 patients the test failed at most in three instances.

The serum protein-bound iodine was also a useful diagnostic aid. However, in five of 28 patients the PBI was normal. The results suggest that the radioactive iodine tolerance test may be more reliable and specific than are serum protein-bound iodine analyses.

Patients in whom Thyrotoxicosis was Suspected but Not Definitely Proved or Disproved

Five patients were referred to this group (Cases 183—187). The clinical and laboratory data are summarized in Table 34.

In Case 183 the eye symptoms dominated the clinical picture. Mild thyrotoxicosis was also considered likely to be present. The urinary excretion of I^{131} was less than normal. Because of the eye symptoms thyroid medication was given for a short period of time, but this made the patient more nervous and produced diarrhea. For experimental purposes the patient was then treated with potassium thiocyanate. While on that medication the patient reported considerable subjective improvement. Objectively there was a fall in BMR from +19 per cent to —7 per cent, gain in weight, and fall in pulse rate from 76 to 58. This appears to be good evidence in favor of thyrotoxicosis.

In Case 184 there was no doubt about the presence of Graves' disease in view of the eye symptoms. The problem was whether or not there was thyrotoxicosis in addition. The excretion of I^{131} was less than normal, while the PBI was normal. The question of thyrotoxicosis was not definitely settled, however. During treatment

with potassium iodide for 10 days the patient improved subjectively, but there was no clear-cut response in BMR or pulse rate. No further follow-up was obtained. The history and clinical findings are best explained by a diagnosis of mild thyrotoxicosis.

In Case 185 also there was little doubt about the presence of Graves' disease. The eyes presented characteristic findings of Graves' disease with unilateral exophthalmos, chemosis, edema of the lids, and limited ocular movements in the exophthalmic eye. Whether she also had thyrotoxicosis was not definitely settled. Both the radioactive iodine test and the PBI indicated thyroid hyperfunction. The response to potassium iodide was not clear-cut. There was subjective improvement and a fall in BMR from +2 to —11 per cent but no gain of weight or drop of pulse rate. The thyroid gland became firmer, however. A mild thyrotoxicosis is probably the best explanation for the findings.

Case 186 had renal impairment with moderate nitrogen retention, but in addition the history and clinical picture were suggestive of thyrotoxicosis. On the basis that thyrotoxicosis was the most likely diagnosis she was treated with 8 mc. of I^{131}. The follow-up was inadequate. The urinary excretion of I^{131} was decreased, but no diagnostic significance could be attached to this result. In the presence of renal damage a low excretion of I^{131} may be due to thyroid hyperfunction or to renal disease or to a combination of both. Unfortunately no analysis of the excretion rate was carried out in this patient.

In Case 187 the diagnosis of thyrotoxicosis was never established. It was apparent that her rheumatic heart disease dominated the clinical picture. There was no apparent benefit from treatment with propylthiouracil. Neither was there any clear-cut response to iodine. Following treatment with 10 mc. of I^{131} there was observed a temporary clinical improvement but no decrease in her BMR. The 48-hour urinary excretion of I^{131} was within normal limits before as well as after the treatment with I^{131}. This case is difficult to evaluate. There may have been a mild thyrotoxicosis, though the evidence is slight.

These five cases show that there are patients in whom a definite diagnosis of thyrotoxicosis is almost impossible to establish. The radioactive iodine tolerance test may become helpful in the evaluation of such patients. The number of cases so far studied is too small to permit any conclusions.

The Use of Radioactive Iodine in the Diagnosis of Toxic Adenoma

It is well established that thyrotoxicosis can be caused by a hyperfunctioning single adenoma of the thyroid. Such an adenoma then is usually called a toxic adenoma. Clinically the thyrotoxicosis in such patients does not differ from that of ordinary Graves' disease, although it has been claimed that cardiovascular symp-

toms are more conspicuous when the thyrotoxicosis is due to a hyperfunctioning adenoma.

Cope, Rawson, and McArthur (1947), when studying the pathophysiology of hyperfunctioning single adenomas of the thyroid, administered tracer doses of radioactive iodine to three such patients. Analyses postoperatively showed that the adenoma had collected much more radioactive iodine than had the uninvolved thyroid tissue.

It may be of interest to demonstrate that the use of radioactive iodine offers a method to establish preoperatively the diagnosis of toxic adenoma.

In the present clinical material of thyrotoxicosis there were seven patients with toxic adenoma (Cases 101, 117, 118, 130, 148, 164, and 166). They have already been discussed from the point of view of the diagnosis of thyrotoxicosis.

Following the administration of radioactive iodine, it was demonstrated by *in situ* measurements with a Geiger-Müller counter, placed directly on the neck, that most of the radioactivity in the thyroid was located in the adenoma. Such measurements were carried out in five patients. The results indicated that the thyrotoxicosis was due to hyperfunction of the adenoma. Postoperative analyses of the amount of radioactive iodine in the adenoma and in the uninvolved tissue proved that the *in situ* measurements had been correct.

These results should be contrasted to the findings in Case 3. This patient had apparent thyrotoxicosis. In the right lobe of the thyroid there was a 4×4 cm. moderately firm nodule while the rest of the gland was judged to be normal in size. Direct measurements over the thyroid showed that there was less radioactive iodine in the large nodule than in the rest of the gland. The results of the *in situ* measurements were confirmed by analyses for radioactive iodine in the resected thyroid. The adenoma was of microfollicular type while the balance of the thyroid showed diffuse hyperplasia. Thus, the direct measurements of the uptake of radioactive iodine demonstrated that in this patient the adenoma was not responsible for the thyrotoxicosis. Similar observations were made in Case 143.

The radioactive iodine thus can be used not only to establish the presence of thyrotoxicosis but also to determine whether the thyroid hyperfunction is due to diffuse hyperplasia or to a hyperfunctioning adenoma.

Chapter IX

THE USE OF THE RADIOACTIVE IODINE TOLERANCE TEST IN THE DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS

A diagnostic test for thyrotoxicosis must be of help not only in establishing the diagnosis but also in excluding it. The latter is the problem that will be taken up in the present chapter. The discussion will deal with the differential diagnosis of endogenous thyrotoxicosis. Thus, thyrotoxicosis produced by an excessive intake of thyroid (thyrotoxicosis factitia) will also be considered as it may be very difficult to differentiate from endogenous (ordinary) thyrotoxicosis.

In hyperophthalmopathic Graves' disease it is important to determine whether or not hyperthyroidism is present. The treatment may differ if it is associated with euthyroidism rather than with hyperthyroidism.

There are a variety of other diseases in which the possibility of thyrotoxicosis must be considered. For example, thyrotoxicosis may give a clinical picture that is difficult to differentiate from cardiovascular disease, psychoneurosis and anxiety states, diseases of the blood and reticuloendothelial system, and other disorders. This is particularly true when a goiter or an elevated BMR or both are present in addition to some extrathyroid disease.

A total of 84 patients is included in this group of diseases that may simulate thyrotoxicosis. Actually, thyrotoxicosis was considered as a possibility only in 63 patients distributed among the various diseases as indicated in Table 11 (p. 49). The remaining 21 cases in which thyrotoxicosis was not suspected were studied in order to have further data on those diseases that often simulate thyrotoxicosis clinically or by laboratory test. Thus, four patients with cardiovascular disease were studied on this basis, ten with anxiety neurosis, and seven with blood diseases.

The problem of differential diagnosis of thyrotoxicosis will be dealt with in the following order:

1. Thyrotoxicosis factitia.
2. Hyperophthalmopathic Graves' disease.
3. Cardiovascular diseases.
4. Anxiety neurosis.

5. Diseases of the blood and reticuloendothelial system.
6. Nonthyrotoxic goiters.
7. Miscellaneous diseases.

1. Thyrotoxicosis Factitia

The diagnosis of thyrotoxicosis factitia (self-induced hyperthyroidism) is rather simple when the patients admit that they are taking large doses of thyroid. Following discontinuation of the medication the symptoms subside in a few weeks and the diagnosis is confirmed. The diagnosis may, however, present great difficulties if the patients do not admit the excessive ingestion of thyroid hormone. Indeed, if such patients take quantities of thyroid in order to manufacture a disease it is most unlikely that they will admit taking it.

The clinical picture of thyrotoxicosis factitia may be indistinguishable from that of ordinary thyrotoxicosis. There are no clinical symptoms or signs that are dependable in the differential diagnosis.

Three patients with secretly self-induced thyrotoxicosis were studied (Cases 176, 177, and 178). In Cases 176 and 178 the diagnosis of thyrotoxicosis factitia was verified, while Case 177 did not admit taking thyroid. Even so there was little doubt about the diagnosis.[1] The use of the radioactive iodine tolerance test in the diagnosis of thyrotoxicosis factitia has been discussed previously on the basis of the observations in Cases 176 and 177 (Skanse and Riggs, 1948). The most important clinical and laboratory data are summarized in Table 35.

Case 176 had been treated for thyrotoxicosis during a period of 10 years before she was referred to the hospital. She had had three thyroidectomies, X-ray therapy, and treatment with thiouracil and iodine without permanent relief of her symptoms of hyperthyroidism. At the time of study she had clinically apparent thyrotoxicosis.

Case 177 had been treated repeatedly for thyrotoxicosis during nine years. She had had subtotal thyroidectomy, thiouracil treatment for more than a year, and repeated courses of iodine, but continued to be thyrotoxic. It should be observed that the previously resected thyroid gland had been reported as normal.

Case 178 will indicate the diagnostic difficulties that these patients may present.

Case 178. A 33-year-old unmarried woman was admitted to the hospital with the diagnosis of thyrotoxicosis. She had been essentially well until two years previously. At that time she became irritable, found it difficult to concentrate on any task, and became easily offended. She had lost about 15 kg. in weight in two years despite a good appetite. She also noted increased jumpiness, tremor of her hands, increased perspiration, persistent tachycardia, palpitation and dyspnea on exertion. She had one episode of ankle edema lasting several weeks. Her family doctor apparently had made a diagnosis of thyrotoxicosis and had treated her with 10 drops of iodine three times daily during four months without relief of symptoms. Later she was treated

[1] In September, 1949, two and a half years after the patient was studied, the family physician uncovered conclusive evidence that this patient had been taking thyroid secretly.

Table 35. Clinical and laboratory dat

Case number	Age Sex	History										Physica		
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor
176	37 ♀	+	+	+	+	+	+	0	0	+	0	Not palpable	w, m	+
177	40 ♀	0	+	+	+	+	+	0	0	+	0	Not palpable	c, d	+
178	33 ♀	+	+	+	+	+	+	0	0	+	+	l, D, s	w, m	+

with thiouracil for two months, also without response. The therapy was discontinued more than three months prior to admission.

The examination showed a well-nourished, uneasy woman, restless in bed and easily upset but cooperative. The skin was warm and moist and flushed over face and neck. There was a tremor of the hands and legs. The thyroid was palpable but not enlarged. No substernal extension was found on X-ray. There was no exophthalmos or other eye signs. Pulse was regular at a rate of 90—100. BP was 130/70.

BMR's were +46, +89, and +90 per cent. PBI was 10.2 μg. per cent. The 48-hour excretion of I^{131} was 94.2 per cent.

Remarks:—This patient presented a characteristic history and clinical picture of thyrotoxicosis. The absence of eye signs was not too disturbing. The absence of goiter was somewhat more disturbing, but thyrotoxicosis without enlargement of the thyroid does occur in certain patients. The PBI was typically elevated. However, the I^{131}-excretion of 94.2 per cent did not fit the diagnosis of endogenous thyrotoxicosis. The combination of an increased excretion of I^{131} and an elevated PBI strongly suggested thyrotoxicosis factitia. *In vivo* measurements demonstrated that hardly any I^{131} was taken up by the thyroid.

The possibility of self-induced thyrotoxicosis was flatly denied by the patient. An interview with her family revealed that she had taken some sort of medicine to reduce weight four years previously. Further investigation revealed that she had purchased thyroid tablets as late as three weeks before admission. When this additional information was reviewed with the patient she admitted that she had taken thyroid tablets more or less continually during four years. The diagnosis of thyrotoxicosis factitia was made possible through the radioactive iodine tolerance test.

Thus, all three patients presented a clinical picture of moderately severe thyrotoxicosis.

The laboratory tests gave the atypical combination of elevated BMR, elevated PBI, and increased excretion of I^{131}. This combination is characteristic of alimentary thyrotoxicosis. Naturally the serum protein-bound iodine analyses cannot differ-

patients with thyrotoxicosis factitia.

amination								Laboratory findings					
	Eyes		Heart								Urinary excretion of I^{131} in per cent		
Exophthalmos	Lid lag	Lid retraction	Enlargement	Fibrillation	Pulse rate	Blood pressure	Edema	Cholesterol mg per cent	BMR per cent	PBI μg per cent	0—24 hours	24—48 hours	Total in 48 hours
+	+	+	0	0	130	130/70	0	227	+51	9.6	94.4	3.8	98.2
0	0	0	+	+	115	140/95	0	167	+33	14.5	85.7	11.6	97.3
0	0	0	0	0	96	130/70	0	131	+75	10.2	87.2	7.0	94.2

entiate between thyroid hormone produced by the patient's own gland and ingested thyroid hormone. The radioactive iodine tolerance test is of great assistance in determining the cause of the elevated "hormonal" iodine. If the elevated PBI is caused by hyperfunction of the thyroid, then the gland's avidity for iodine is increased, and it can be demonstrated directly by the *in vivo* measurement of the uptake of I^{131} or indirectly by a decreased urinary excretion of I^{131}. If the elevated PBI is caused by prolonged thyroid medication, then the thyroid will have a decreased avidity for iodine and the urinary excretion of I^{131} will be increased.

The combination of elevated BMR, elevated PBI, and increased excretion of I^{131} is not absolutely pathognomonic of thyrotoxicosis factitia. However, the other conditions in which the same laboratory pattern may be observed do not usually cause any diagnostic confusion.

A similar pattern may be observed in patients with endogenous thyrotoxicosis during treatment with thiouracil or iodine before the patient is brought into a euthyroid state. The administration of contrast media containing iodine to thyrotoxic patients will give a similar picture. The reasons for the high excretion of I^{131} under these circumstances were discussed in Chapter VII. However, the other situations in which the same laboratory pattern may be observed are of little clinical significance.

2. Hyperophthalmopathic Graves' Disease with Euthyroidism

In Graves' disease the eye symptoms may be of all degrees of severity. They may be completely absent or may dominate the clinical picture. This variable severity of eye symptoms may be associated with most different degrees of thyrotoxicosis. Thus, a form of Graves' disease has been recognized in which the eye symptoms dominate the clinical picture and thyrotoxicosis is absent or minimal. Means

Table 36. **Clinical and laboratory data in patients with hyperophth**

Case number	Age Sex	History										Physical examination										
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes			Heart		Pulse rate	Blood pressure	
															Exophthalmos	Lid lag	Lid retraction	Enlargement	Fibrillation			
348	55 ♂	0	0	0	0	+	0	0	+	0	0	1, D, s	n	0	+	+	+	0	0	72	120/60	
349	41 ♂	0	+	+	0	0	0	0	+	+	0	1, D, s	n	0	+	0	0	0	0	84	120/80	
350	68 ♀	0	0	0	0	0	0	0	+	0	0	1, D, s	n	0	+	0	+	0	0	74	160/80	
351	58 ♂	0	0	0	+	0	0	0	+	0	0	Not palpable	n	0	+	+	+	0	0	74	120/85	
229	54 ♀	0	0	0	0	0	0	0	+	0	0	1½, D, f	n	0	+	0	0	0	0	76		
230	36 ♀	0	0	0	0	0	0	0	+	0	0	1½, D, f	n	0	+	0	0	0	0	90	115/80	

(1948) uses the term hyperophthalmopathic Graves' disease for this syndrome. Malignant exophthalmos, exophthalmic ophthalmoplegia, and other terms have also been used. As thyroidectomy should be avoided in hyperophthalmopathic Graves' disease, it is important to differentiate this syndrome from ordinary Graves' disease.

Hertz and Roberts (1942) observed that three of five patients with hyperophthalmopathic Graves' disease excreted more of a test dose of radioactive iodine in the urine than did six patients with classic Graves' disease. They suggested that the radioactive iodine excretion might be used to distinguish between these two types of patients.

In the previously discussed patients with thyrotoxicosis three patients (Cases 26, 49, and 56) were observed who had severe eye symptoms with diplopia, chemosis, and edema as in hyperophthalmopathic Graves' disease. These patients, however, also had readily recognized moderately severe thyrotoxicosis. The urinary excretion of I^{131} was also typical of thyrotoxicosis. The planning of the treatment, therefore, was no problem. Case 185 had severe eye symptoms which probably were combined with mild thyrotoxicosis (see p. 130).

Four patients with hyperophthalmopathic Graves' disease with euthyroidism were also studied (Cases 348—351). The clinical and laboratory data are summarized in Table 36. Thyrotoxicosis was most unlikely on clinical grounds. The BMR was normal. The urinary excretion of I^{131} was normal. These observations con-

athic Graves' disease and in patients with unilateral exophthalmos.

Laboratory findings					Diagnosis	Remarks
BMR per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent				
		0—24 hours	24—48 hours	Total in 48 hours		
+4	6.1	54.7	4.5	59.2	Hyperophthalmopathic Graves' disease	Globe lag, puffiness, paralysis of upward gaze, injection of lateral recti.
—1		81.7	6.1	87,8	»	Chemosis, edema of lids, periorbital edema.
—5	4.9	68.9	8.9	77.8	»	Chemosis, edema of lids, injection of sclerae.
+5	3.8	60.2	7.9	68.1	»	Globe lag, edema of lids, injection of sclerae, diplopia on upward gaze.
+3		61.7	5.0	66.7	Unilateral exophthalmos + Nontoxic goiter	
—1		51.1	2.5	53.6	»	

firm the suggestion of Hertz and Roberts (1942) that the radioactive iodine excretion may be used to differentiate this type of Graves' disease from the ordinary type. It should be remembered, however, that this differential diagnosis usually can be made clinically.

Radioactive iodine tolerance tests were also carried out in two patients (Cases 229 and 230) with unilateral exophthalmos and goiter but without symptoms of thyrotoxicosis (Table 36). As expected, the urinary excretion of I^{131} was normal.

These results indicate that the radioactive iodine tolerance test may be employed to determine whether or not thyrotoxicosis is present in patients with hyperophthalmopathic Graves' disease, if there is any doubt clinically.

3. Cardiovascular Diseases

The effect of the thyroid hormone on the cardiovascular system is well recognized. Hyperfunction of the thyroid may be manifested mainly by cardiovascular symptoms. This form of masked hyperthyroidism is well-known but nevertheless often presents diagnostic problems. Previously in this paper it was shown that the radioactive iodine tolerance test may be used successfully in the diagnosis of thyrotoxicosis when the clinical picture is dominated by symptoms from the cardiovascular system, or when thyrotoxicosis is associated with organic cardiovascular disease.

Table 37. **Clinical and laboratory d**

Case number	Age Sex	History										Physical examination									
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes			Heart		Pulse rate	Blood pressure
															Exophthalmos	Lid lag	Lid retraction	Enlargement	Fibrillation		
352	46 ♂	+	0	0	+	0	0	0	0	+	0	1, D, s	d	0	0	0	0	+	0	60	210/90
231	75 ♀	+	0	0	0	+	+	+	0	0	0	2, N, f	w, m	0	0	0	0	+	+	80	200/90
353	47 ♀	0	0	+	0	+	+	0	0	0	0	1, D, s	w, m	0	0	0	0	+	0	76	160/100
232	58 ♂	0	0	+	+	0	+	0	0	0	0	2, N, f	w, m	+	0	+	+	+	0	100	165/90
354	70 ♂	0	0	0	0	+	+	0	0	0	0	1, D, s	n	0	0	0	0	0	0	96	130/90
355	35 ♀	0	0	0	+	+	+	0	0	+	0	Not palpable	n	+	0	0	+	+	0	96	135/60
233	68 ♀	+	0	+	+	0	0	0	0	0	0	2, N, f	n	0	0	+	+	+	+	84	170/100
356	52 ♂	0	0	+	0	+	0	0	0	+	0	1, D, s	n	+	0	+	0	+	0	70	110/60
357	22 ♂	+	0	0	0	+	+	0	0	0	0	1, D, s	n	+	0	0	0	+	0	90	165/95
234	67 ♀	0	0	+	0	0	+	0	0	0	0	1½, D, s	n	0	0	0	0	0	0	120	150/100
235	54 ♀	0	0	0	+	+	+	0	0	0	0	1½, N, f	n	0	0	0	0	+	+	76	140/90
358	57 ♀	+	0	0	+	0	+	0	+	+	0	1, D, s	n	+	+	0	0	+	+	100	200/110
359	49 ♂	+	0	0	+	+	0	0	0	0	+	1, D, s	n	+	0	0	0	+	0	94	190/100
360	60 ♀	0	0	0	0	0	+	0	0	0	0	1, D, s	n	+	0	0	0	0	0	90	220/100
361	42 ♀	0	0	0	0	0	0	0	0	0	0	1, D, s	n	0	0	0	0	0	0	88	240/135
236	52 ♀	+	0	+	+	+	0	0	0	+	0	2–3, N, s	n	+	0	0	0	+	0	90	210/125
362	54 ♀	0	0	0	0	+	+	0	0	0	0	1, D, s	w, m	0	0	+	0	+	0	80	210/110
237	39 ♀	0	0	0	0	0	+	0	0	+	+	2, D, f	n	0	0	0	0	0	0	100	180/90
238	64 ♂	+	0	0	0	+	+	0	0	+	0	1½, N, f	w	+	0	+	0	0	0	124	210/100
239	27 ♀	0	0	0	0	0	0	0	0	0	0	2, D, s	n	+	0	0	0	0	0	82	175/125

Cardiovascular disease may present a clinical picture which can simulate hyperthyroidism. Thyrotoxicosis must be even more seriously considered if a goiter is present in addition. The basal metabolic rate has a limited value in cardiac and hypertensive diseases, as such diseases in themselves are capable of raising the BMR. There is no doubt that methods designed to aid in the differential diagnosis between cardiovascular disease and thyrotoxicosis are needed. The present study will demonstrate the value of the radioactive iodine tolerance test in excluding thyrotoxicosis in patients with various cardiovascular diseases.

Twenty patients (Cases 231—239 and 352—362) were studied. The clinical and laboratory data as well as the final diagnoses are presented in Table 37. The majority of the patients had coronary heart disease, rheumatic heart disease, hypertensive cardiovascular disease, or essential hypertension. Nine patients were in congestive

atients with cardiovascular diseases.

Laboratory findings					Diagnosis
BMR per cent	PBI µg per cent	Urinary excretion of I^{131} in per cent: 0—24 hours	24—48 hours	Total in 48 hours	
+10		48.0	8.2	56.2	Coronary heart disease.
+16		54.5	10.4	64.9	Coronary heart disease + Congestive failure.
+14	4.2	44.9	17.7	62.6	» » » + » »
+20	4.9	50.5	10.4	60.9	Myocardial infarction.
		59.6	6.3	65.9	Arteriosclerotic heart disease + Congestive failure + Pulmonary fibrosis.
+ 9		61.0	5.5	66.5	Rheumatic heart disease + Congestive failure.
+ 2	4.4	59.2	4.1	63.3	Rheumatic heart disease + Angina pectoris + Congestive failure + Diabetes mellitus + ? Subacute bacterial endocarditis.
+24	5.4	57.5	9.7	67.2	Rheumatic heart disease + Angina pectoris.
+40	3.4	66.1	6.0	72.1	Coarctation of aorta + Patent interventricular septum.
	5.1	57.0	5.7	62.7	Tachycardia + Fracture of right femur neck.
+ 8	6.1	55.1	6.5	61.6	Auricular fibrillation + Diabetes mellitus + ? Cirrhosis of the liver.
+ 4	5.6	43.4	9.7	53.1	Hypertensive cardiovascular disease + Congestive failure.
+49	2.8	52.7	3.0	55.7	» » » + Parkinsonism.
+12	5.2	54.4	3.2	57.6	» » »
+18	5.8	41.8	5.9	47.7	» » » + Congestive failure.
+24	5.0			63.0*	» » » + » »
+ 7	3.9	50.3	11.8	62.1	» » » + » »
+16	5.2	67.3	6.5	73.8	Essential hypertension + Vasomotor instability.
+39	10.3	73.1	16.4	89.5	Essential hypertension.
+21	6.3	47.9	5.3	53.2	» »

* Calculated from *in vivo* measurements.

failure. Several of the patients gave a history that was consistent with thyrotoxicosis although it was not typical. The thyroid was enlarged in nine patients. The pulse rate was ≥ 80 in 16 patients. Auricular fibrillation was observed in four cases. The basal metabolic rate was elevated in six patients. One would hardly expect the BMR to be normal if thyrotoxicosis and cardiac disease were present together. However, it has been shown that this may occur (p. 125).

In 16 of the 20 patients in this group the diagnosis of thyrotoxicosis was considered on clinical grounds. It should be admitted that thyrotoxicosis was a rather remote possibility in several patients, for example Cases 357 and 239. In most cases the important point was to determine if thyrotoxicosis was present in addition to organic cardiovascular disease. In other patients, for example Cases 234 and 235, the question arose whether the cardiovascular symptoms were caused entirely by thyrotoxicosis.

The possibility of thyrotoxicosis was raised because of the combination of auricular fibrillation and goiter (Cases 231 and 235) or goiter and tachycardia (Case 234). Case 355 had had a subtotal thyroidectomy one year prior to this study and returned to the hospital in congestive failure. In Cases 232, 352, 353, 359, 236, and 237 the history was somewhat suggestive of thyrotoxicosis as was the clinical picture because of such findings as goiter (Cases 232, 236, and 237), warm and moist skin (Cases 232 and 353), tremor (Cases 232 and 236), and elevated BMR (Cases 359 and 236). Case 239 presented the combination of goiter and elevated BMR. In case 357 the elevated BMR was due to coarctation of the aorta and in Case 359 probably to Parkinsonism. The diagnostic problems may be illustrated by four case reports.

Case 356. A 52-year-old man complained chiefly of pain in the left chest of two years' duration. For three years he had noticed shortness of breath and a burning nonradiating pain in the precordial region on exertion. The precordial pain was relieved by nitroglycerine. There was no recent weight loss. He also complained of easy fatiguability, intolerance to heat, and nervousness.

The examination revealed a fine tremor of the fingers, a thyroid of normal size, and a slight lid lag. The heart was enlarged, predominantly in the region of the left ventricle. There was a loud, harsh aortic systolic murmur and a soft blowing aortic diastolic murmur, and an apical systolic murmur. The pulse was regular at a rate of 68—72. BP was 110/60. ECG showed marked evidence of left ventricular strain. The liver was felt 3 cm. below costal margin, but there was no ankle edema.

BMR was +24 and one month later +30 per cent. PBI was 5.4 μg. per cent. The 48-hour excretion of I^{131} was 67.2 per cent.

Diagnosis: Rheumatic heart disease (aortic stenosis and insufficiency, mitral insufficiency) + Angina pectoris.

Remarks:—Although the diagnosis of primary heart disease was obvious in this case, the question of thyrotoxicosis in addition was raised. The elevated BMR's were slightly suggestive, but the history and clinical findings were not characteristic. The normal excretion of I^{131} and the normal PBI indicated a euthyroid state. The subsequent course did not present any further evidence of thyrotoxicosis. This case is similar to the type of patients described by Smith and Levine (1947). They observed a few patients in whom aortic stenosis was associated with persistent elevation of the basal metabolic rate and certain symptoms and signs suggestive of thyrotoxicosis, but in whom thyroidectomy demonstrated a normal thyroid.

Case 233. A 68-year-old woman complained chiefly of shortness of breath of two years' duration. She had noted ankle edema for 15 months. Three months prior to entry she began to have a sharp pain beginning at the base of the left breast and radiating to the nipple, coming on with exertion, cold, or emotional stress. Her appetite had been poor and she had lost weight. All her life she had been intolerant to hot weather and had perspired more than normal.

The physical examination revealed a thyroid of about 2 × normal size which was nodular and moderately firm. There was no definite exophthalmos but stare and lid and globe lag. The heart was enlarged, particularly the left auricle. A heaving apical impulse was palpated 14 cm. to the left of the midsternal line. There was a mitral diastolic murmur. Pulse was irregular at a rate of 84. ECG showed auricular fibrillation and left axis deviation. BP was 170/100. There

were moist inspiratory râles over both lung bases and there was slight ankle edema. The liver was not felt. The spleen was just palpable.

The urine contained sugar. The Hgb was 17.0 g. per cent and the RBC was 6,700,000. The WBC was 17,700 with 64 per cent neutrophils and 31 per cent lymphocytes. Fasting blood sugar was 190 and 218 mg. per cent. The NPN was 34 mg. per cent. Repeated blood cultures were negative. BMR's were +4, ±0, and +1 per cent. PBI was 4.4 μg. per cent. The 48-hour excretion of I^{131} was 63.3 per cent and in a repeated test 58.8 per cent.

On treatment with low sodium diet, digitalis, ammonium chloride, and mercurials she improved considerably. She was given potassium iodide for two weeks without any change in the clinical picture. She continued to run a persistent low grade fever which was never satisfactorily explained unless on the basis of active rheumatic fever or subacute bacterial endocarditis.

Diagnosis: Rheumatic heart disease with mitral stenosis and auricular fibrillation + Arteriosclerotic heart disease + Angina pectoris + Congestive failure + ? Subacute bacterial endocarditis + Diabetes mellitus + Nontoxic nodular goiter.

Remarks:—It was obvious that this patient primarily had organic heart disease. It was more difficult to determine whether or not there was superimposed thyrotoxicosis. The history of weight loss (though with poor appetite), intolerance to heat, and increased perspiration was somewhat suggestive of thyrotoxicosis as were the findings of goiter and eye signs (lid retraction and lid lag). The auricular fibrillation could be explained on the basis of either disease.

The subsequent course of this patient's illness was not in keeping with a diagnosis of thyrotoxicosis, and the laboratory tests were in agreement with this.

Case 358. A 57-year-old woman complained chiefly of increasing shortness of breath. She had a history of hypertension of 18 years' duration. She had lost 20 kg. in weight on a reduction diet one year before admission. Her appetite had been good. Five or six years before admission her eyes became prominent and she experienced some diplopia. Subsequently her eyes receded to some degree spontaneously. She had always been a nervous and irritable person. For many years she had perspired easily, but there was no real heat intolerance. For several years she had been bothered with palpitation and irregular heart action. In the weeks preceding admission her legs had gradually become swollen.

The examination showed a slightly orthopneic woman. There was a minimal tremor of the extended fingers. The thyroid was not enlarged. There was definite exophthalmos bilaterally but no other eye signs. The heart was enlarged, particularly in the region of the left ventricle. Pulse was irregular at a rate of 100. BP was 200/110. The liver was palpable 6 cm. below costal margin. There was moderate pitting edema of ankles and calves.

The urine was normal. BMR was +4 per cent. PBI was 5.6 μg. per cent. The 48-hour excretion of I^{131} was 53.1 per cent.

On treatment with digitalis, diuretics, and low sodium diet the patient improved considerably. On examination twenty months later there was still exophthalmos but no symptoms or signs of thyrotoxicosis.

Remarks:—Although the history and clinical picture were not typical of thyrotoxicosis, such symptoms as increased sweating, nervousness, proptosis of the eyes, and auricular fibrillation made it necessary to consider the possibility of thyrotoxicosis. The normal laboratory findings presented strong evidence against thyrotoxicosis. The subsequent course made it certain that she suffered from hypertensive cardiovascular disease only.

Case 238. A 64-year-old man complained chiefly of easy fatiguability, weight loss, and anorexia of five months' duration. He had had hypertension for at least six years. For five months he had noted emotional instability and nervousness. He had lost seven kg. in weight.

The examination revealed warm but not abnormally moist skin, a fine tremor of the extended fingers, and a thyroid of about $1\ ^1/_2 \times$ normal size which was nodular and quite firm. There was no exophthalmos but a bilateral lid lag. There was a loud systolic murmur along the left sternal border, loudest over aortic area. $A_2 > P_2$. Pulse was regular at a rate of 124. BP was 210/100. There was slight pitting edema of the ankles.

Urine was normal. BMR's were +48, +37, and +33 per cent. PBI's were 9.2 and 11.4 μg. per cent. The 48-hour excretion of I^{131} was 89.5 per cent. On an adrena ine tolerance test there was a rise of only 10 mm. of the blood pressure. The administration of histamine caused no secondary rise of the blood pressure. An intravenous pyelogram was normal.

Since it was felt that thyrotoxicosis was the most likely diagnosis, the patient was prepared for surgery. It should be noted that despite treatment with thiouracil for six weeks and potassium iodide for ten days the BMR did not fall more than from about +35 per cent to about +15 per cent. At operation the thyroid gland was found to be small and fibrotic, and did not have the appearance of a toxic gland. The major part of the right lobe, weighing only five grams, was resected. The microscopic examination showed no signs of hyperplasia.

On examination four months later the patient felt improved but was still nervous. He had gained nine kg. in weight and his appetite had improved. BMR was +18 per cent. Pulse rate was 100 and BP was 200/100. PBI was 5.2 μg. per cent.

Remarks:—This was a very puzzling case. The history of easy fatiguability, weight loss, nervousness, and palpitation was compatible with thyrotoxicosis, but the anorexia and lack of intolerance to heat were atypical. The clinical picture was consistent with thyrotoxicosis as was the elevated BMR. The elevated PBI favored thyrotoxicosis. On the other hand, the very slow response to thiouracil and particularly the complete absence of thyroid hyperplasia microscopically were strong evidence against thyrotoxicosis. The high excretion of I^{131} did not indicate hyperfunction. That the patient did not have thyrotoxicosis was also supported by the fact that his symptoms remained relatively unchanged postoperatively, except for gain in weight. The possibility of pheochromocytoma was raised but there was no exploration of the adrenals. There was nothing found to account for the elevated PBI. The possibility of thyroid administration was ruled out with reasonable certainty. The diagnosis in this case was never satisfactorily established. However, the final decision was that there had been no thyrotoxicosis. The I^{131}-test was correct, while the PBI was misleading.

The 48-hour urinary excretion of I^{131} was in no case below normal. It varied between 47.7 per cent and 89.5 per cent with an average of 63.0 ± 2.0 per cent. This average does not differ significantly from that of normal individuals. The individual values were within $\pm 3\sigma$ of the normal mean except in one patient (Case 238) whose excretion was slightly higher than normal. The 0—24 hour excretion was in the normal range in all cases. The 24—48 hour excretion was higher than normal in three patients (Cases 238, 353, and 362). In Cases 238 and 353 the second-day excretion was as high as in myxedema. The reason for this delay in excretion is not

entirely clear. It might have been due to renal impairment as it occurred in patients with hypertensive cardiovascular disease. *From the diagnostic point of view it should be emphasized that in no patient did the radioactive iodine tolerance test indicate thyrotoxicosis.*

The serum protein-bound iodine, determined in 16 patients, was normal in 15 patients, and elevated in repeated tests in one patient (Case 238, see above).

The results show that the radioactive iodine tolerance test can successfully be used to exclude thyrotoxicosis in patients with cardiovascular disease in whom the history and clinical findings are suggestive of thyrotoxicosis. The test is far superior to the determination of the basal metabolic rate and is at least as reliable as the determination of the serum protein-bound iodine.

4. Anxiety Neurosis

Anxiety neurosis, neurocirculatory asthenia, effort syndrome, autonomic imbalance, vegetative neurosis, and other terms have been used for a syndrome with a variety of nervous, cardiovascular, respiratory, and muscular symptoms predominating. A recent description of the clinical picture and a definition of this syndrome were given by Cohen, White, and Johnson (1948). Striking features of the syndrome are nervousness, irritability, shakiness, dizziness, shortness of breath, easy fatigue, and emotional stress. Abnormal physical findings are few. High resting pulse rate, flushed face, and tremor of the fingers occur in a high percentage of the cases. The basal metabolic rate is within normal limits.

Several of these symptoms are similar to those of mild thyrotoxicosis. It is therefore not surprising that the differential diagnosis between thyrotoxicosis and anxiety neurosis may present problems. This is especially true when a goiter is present or when the BMR is elevated on some other basis. Sometimes the clinical picture may simulate thyrotoxicosis even more closely.

It is not within the scope of the present paper to discuss the clinical diagnosis of anxiety neurosis. The aim is to demonstrate the value of the radioactive iodine tolerance test in excluding thyrotoxicosis in patients with anxiety neurosis. In doubtful cases the diagnosis of anxiety neurosis was made only after prolonged observation and psychiatric consultation.

Twenty-two patients were studied (Cases 240—249 and 363—374). The most important clinical and laboratory data are presented in Table 38. Nervousness and palpitation were the most frequent symptoms. Nervousness was the chief complaint in half of the patients and was present in all but one patient. In the other patients palpitation or fatigue was the dominant symptom. Loss of weight appeared in nine patients, but increased appetite occurred in only four patients. Actually, the appetite was decreased in nine patients. Goiter was present in ten cases. Signs suggestive of hyperthyroidism, such as warm and moist skin, tremor, and tachycardia,

Table 38. Clinical and laboratory data

Case number	Age Sex	History										Physica				
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes	
															Exophthalmos	Lid lag	Lid retraction
240	33 ♀	+	0	0	0	+	+	0	0	+	0	2½—3, D, s	n	+	0	0	0
363	58 ♀	+	0	+	+	0	+	0	0	+	0	1, D, s	c, m	+	0	0	0
241	37 ♀	+	0	+	+	+	+	0	0	+	+	2, D, s	n	+	0	+	0
364	49 ♀	0	0	0	+	+	+	0	0	0	0	1, D, s	c, d	0	0	0	0
242	26 ♀	+	0	0	0	+	0	0	0	+	0	2, D, s	n	0	0	0	0
243	56 ♀	0	0	0	0	0	+	+	0	+	0	3, N, f	m	0	0	0	0
244	27 ♂	0	0	0	+	0	+	+	0	+	0	2, N, s	w, d	+	0	0	0
365	46 ♀	+	0	0	0	+	+	+	0	+	0	1, D, s	d	0	+	+	+
366	35 ♂	0	0	0	+	0	+	0	0	+	0	1, D, f	m	+	0	0	0
245	35 ♀	+	+	+	+	+	+	+	0	+	0	2, N, f	w, d	0	0	0	0
367	26 ♀	+	+	0	+	+	+	+	+	+	0	1, D, s	n	0	0	+	+
246	42 ♀	0	0	0	0	0	+	0	0	+	0	1½, D, f	n	0	0	0	0
368	25 ♂	0	0	0	+	0	+	0	+	+	+	1—1½, D, s	w, d	+	+	0	0
369	52 ♀	0	0	0	0	0	+	0	0	+	0	1, D, s	n	0	0	0	0
370	31 ♀	+	0	0	0	0	0	0	0	+	0	1, N, s	n	0	0	0	0
247	31 ♀	0	+	0	+	+	+	+	0	+	+	1½, N, f	n	0	0	0	0
371	46 ♀	+	0	+	+	+	0	0	0	+	0	Not palpable	w, m	+	0	0	0
248	40 ♀	0	0	0	0	0	+	+	0	+	+	1½, N, s	m	0	0	0	0
372	67 ♀	0	0	+	0	+	+	0	0	+	+	1, D, s	c, m	+	0	+	0
249	37 ♂	0	+	+	0	0	0	0	0	+	0	2, D, s	n	+	0	0	0
373	22 ♀	0	0	+	+	0	0	0	0	+	0	1—1½, D, s	n	+	0	0	+
374	35 ♀	0	0	+	+	0	+	0	0	+	0	1—1½, D, s	n	+	0	0	0

were found in a number of patients as is indicated in the table. The basal metabolic rate was elevated in one patient.

Thyrotoxicosis was not seriously suspected in all patients. It could be fairly well excluded in at least ten patients without special studies or prolonged observation. However, histories suggestive or even rather characteristic of thyrotoxicosis in combination with goiter (10 cases) or tachycardia (4 cases) and sometimes other signs as well (warm and moist skin, tremor) made it necessary to consider the possibility of mild and atypical thyrotoxicosis being present.

The differential diagnostic problems may be illustrated by three case reports:

patients with anxiety neurosis.

amination					Laboratory findings						
Heart		Pulse rate	Blood pressure	Edema	Cholesterol mg per cent	BMR per cent	PBI μg per cent	Urinary excretion of I^{131} in per cent			Complicating disease
Enlargement	Fibrillation							0—24 hours	24—28 hours	Total in 48 hours	
0	0	60	100/80	0		± 0		71.2	5.2	76.4	Nontoxic goiter.
0	0	100	150/100	0	219	+17	5.1	46.7	3.4	50.1	Paget's disease.
0	0	72	110/60	0	189	+ 7	5.1	82.3	2.9	85.2	? Chronic bronchiectasis + Nontoxic goiter.
0	0	80	145/80	0		— 9		52.2	2.5	54.7	
0	0	82	110/60	0		+ 5		68.6	2.6	71.2	Nontoxic goiter.
0	0	76	195/110	0	221	— 4	5.8	62.6	1.5	64.1	» »
0	0	76	120/80	0		+27		64.4	4.1	68.5	» »
0	0	80	120/85	0	305	± 0	4.7	50.0	8.1	58.1	Diabetes mellitus + Fibroids of the uterus + ? Ovarian cyst.
0	0	120	150/90	0	240	+ 8	7.2	56.0	1.8	57.8	
0	0	76	130/85	0	174	— 2	5.0	49.2	2.9	52.1	Nontoxic goiter.
0	0	84	110/70	0	147	+ 2	4.7	68.3	2.5	70.8	
0	0	80	140/80	0		—16	4.8	81.0	9.8	90.8	Nontoxic goiter + Paroxysmal tachycardia.
0	0	80	145/75	0		— 4	4.1	65.8	4.5	70.3	
0	0	104	170/100	0		+ 1		67.0	9.6	76.6	
0	0	64	130/90	0		+20	5.4	48.8	3.9	52.7	
0	0	68	135/95	0	231	+12	5.9	54.7	3.0	57.7	Nontoxic goiter.
0	0	110	155/100	0	195	+14	5.9	87.4	10.9	98.3	Angina pectoris.
0	0	68		0		+ 6	7.5	56.6	2.7	59.3	Nontoxic goiter.
0	0	78	230/100	0	185	+11		43.9	5.1	49.0	Essential hypertension.
0	0	62	110/80	0	227	— 1	4.3	55.5	1.1	56.6	Nontoxic goiter.
0	0	72	100/70	0		— 3	4.3	52.8	2.9	55.7	
0	0	80	120/80	0	189	— 3		68.5	4.4	72.9	

Case 365. A 46-year-old unmarried female schoolteacher complained chiefly of weakness and tenseness of six weeks' duration. The patient was well until 1939 when she developed a mild diabetes that was controlled by diet. In 1940 she developed thyrotoxicosis. She refused operation and was treated with X-rays, but in 1942 a subtotal thyroidectomy was performed. In 1945 she was found to have recurrence of thyrotoxicosis and had a second thyroid operation. Postoperatively she felt improved but continued to be nervous. In the spring of 1947 she developed symptoms which she attributed to a recurrence of the thyroid disease. The episode began as a "shooting" through the nerves in her thyroid, a sensation of electricity through her body to the back of her neck, a feeling which had been present intermittently. Her "nerve force" became completely dissipated and she felt increasingly weak physically but extremely tense mentally. She also described a feeling of fullness in her neck and a cough which she attributed to a

"slow strangulation" along with brief episodes of dyspnea when she was especially nervous. She complained of intolerance to cold and of dryness of the skin and hair. Her appetite had been poor and she had lost three kg. in two months. Her diabetes was treated with 36 units of protamine zinc insulin daily.

The physical examination was negative except for dry skin, slight exophthalmos, slight lid lag, and fibroids of the uterus.

Fasting blood sugar was 132 mg. per cent. BMR was zero. PBI was 4.7 μg. per cent. The 48-hour excretion of I^{131} was 58.1 per cent.

Remarks:—In view of two previous episodes of thyrotoxicosis the possibility of recurrence had to be considered. Her later history and the clinical findings were not consistent with recurrence of thyrotoxicosis. The laboratory data indicated a euthyroid state. She was studied by a psychiatrist who felt that her symptoms were best explained on the basis of psychoneurosis. On examination three months later her symptoms remained unchanged. There was no further evidence of thyrotoxicosis.

Case 368. A 25-year-old machine shop worker complained chiefly of nervousness and tremor of four years' duration. Seven years before admission rheumatic heart disease with mitral involvement was diagnosed. His nervousness started at a time when he was given a more lucrative position as an inspector which involved a great change in his responsibilities and living conditions. He became irritable and tense and felt uneasy with friends as well as with strangers. He was much concerned about a coarse tremor of his hands. He began to sweat more than previously, but there was no real intolerance to heat. Occasionally he was bothered with palpitation. His eyes had always been somewhat prominent but there was no recent increase of the prominence. After return to his old work in the machine shop he felt better for some period of time but when he was changed from night to day shift his symptoms of tremor, palpitation, perspiration, and tenseness increased again. There was no weight loss.

The examination revealed a tense, unstable man. The skin was warm and dry except for moist palms and soles. There was a marked coarse tremor of the hands. The thyroid was 1—1 $^1/_2$ × normal size. There was bilateral exophthalmos but no other eye signs. The heart was of normal size with mitral systolic and diastolic murmurs. Pulse was regular at a rate of 80. BP was 145/75.

BMR's were —1 and —7 per cent. PBI was 4.1 μg. per cent. The 48-hour excretion of I^{131} was 70.3 per cent.

The patient was treated with psychotherapy and improved at least temporarily. He continued, however, to be anxious and nervous but was able to handle his work. On examination seven months later there was no essential change in the clinical picture. The BMR was —7 per cent.

Remarks:—The history was best explained on the basis of anxiety neurosis, but the finding of exophthalmos made it necessary to consider the possibility of thyrotoxicosis.

After prolonged observation several psychiatrists were of the definite opinion that this patient suffered from a severe anxiety neurosis. The laboratory tests also indicated the absence of hyperthyroidism.

Case 371. A 46-year-old housewife complained chiefly of malaise and dyspnea of nine months' duration. Six months before admission she began to complain of substernal compression which accompanied exercise and was relieved by rest. She was given nitroglycerine with relief. Later she also developed dyspnea on exertion and slight ankle edema. During the three months prior

to admission her most prominent symptoms were a feeling of warmth and intolerance to heat. She complained of nervousness, irritability, and insomnia. She had several episodes of syncope. She had lost 13 kg. in weight in nine months. Her appetite had been poor.

The physical examination was negative except for warm and moist skin, a fine tremor of the hands, and a pulse rate of 110. BP was 155/100.

BMR's were initially +49, +25, and +20 per cent but fell in two weeks to —5 and —10 per cent. PBI was 5.9 μg. per cent. The 48-hour excretion of I^{131} was 98.3 per cent.

After the diagnosis of thyrotoxicosis was ruled out the patient was followed by the psychiatric service. They diagnosed an anxiety neurosis primarily on the basis of family difficulties. On examination about one year after her hospital admission she had gained eight kg. in weight. There was no evidence of thyrotoxicosis.

Diagnosis: Anxiety neurosis + Angina pectoris.

Remarks:—The history was compatible with thyrotoxicosis although not characteristic. The findings of tachycardia, warm and moist skin, and tremor were suggestive of thyrotoxicosis. The laboratory tests did not favor thyrotoxicosis, although the BMR was elevated initially. A diagnostic trial with potassium iodide did not lower the pulse rate. The very high excretion of I^{131} raised the possibility of thyrotoxicosis factitia, as did her falling BMR while staying in the hospital. However, the PBI was normal and the tachycardia remained unchanged despite the fall of the BMR to normal values. No reason for the very high excretion of I^{131} was found.

The radioactive iodine tolerance test in no case indicated thyrotoxicosis. The 48-hour excretion of I^{131} averaged 65.9 per cent which is identical with that of normal subjects. It was within the normal range in 20 patients and higher than normal in two patients. No explanation for the two latter values was found. In Case 371 the possibility of secret ingestion of thyroid was suspected but could not be proved.

The serum protein-bound iodine, determined in 15 patients, was normal in every patient.

The results show that the radioactive iodine tolerance test and the serum protein-bound iodine are reliable aids in the differential diagnosis of thyrotoxicosis and anxiety neurosis.

5. Diseases of the Blood and Reticuloendothelial System

It is well-known that the basal metabolic rate may be elevated in polycythemia, leukemia, lymphoma, and similar diseases.

By means of the radioactive iodine tolerance test the thyroid function was evaluated in ten patients with various diseases of this type (Cases 250—252 and 375—381). The results are presented in Table 39. The urinary excretion was normal in every patient. These findings confirm previous observations that the elevated basal metabolic rate in such diseases is not caused by thyroid hyperfunction.

The clinical picture in this type of disease is usually so different from that of thyrotoxicosis that the differential diagnosis is easy. Occasionally, however, the

Table 39. The laboratory tests in patients with diseases of the blood and reticulo-endothelial system.

Case number	Age Sex	Diagnosis	Thyroid size and type	BMR per cent	PBI μg per cent	Urinary excretion of I^{131} in per cent		
						0—24 hours	24—48 hours	Total in 48 hours
375	62 ♀	Polycythemia vera	1, D, s	+31		64.0	8.8	72.8
376	12 ♀	Acute leukemia	1, D, s			49.6	3.1	52.7
377	38 ♀	Chronic myelogenous leukemia	1, D, s	+21		53.3	3.2	56.5
250	61 ♀	» » »	2, N, f	+43				58.5*
378	48 ♂	» lymphatic »	1, D, s	+ 7		40.5	9.5	50.0
379	62 ♂	» » »	1, D, s	+ 2		56.7	2.3	59.0
380	54 ♀	Malignant lymphoma (clasmatocytic type)	1, D, s	—15		60.7	6.4	67.1
251	31 ♂	Lymphoblastoma	2, D, f		6.2	57.8	3.9	61.7
252	40 ♀	Hodgkin's disease	2, D, f	+18	5.8	73.4	5.4	78.8
381	62 ♀	Banti's syndrome	1, D, s	+36		54.3	5.6	59.9

* Calculated from *in vivo* measurements.

clinical picture may imitate that of thyrotoxicosis. Diagnostic problems are particularly likely to arise if goiter is present in addition.

In the present study there were three patients in which the possibility of thyrotoxicosis had to be considered. In Case 250 a chronic myelogenous leukemia was associated with a goiter. The radioactive iodine tolerance test was of value in confirming the clinical impression of nontoxic goiter. In Case 252 the history and clinical findings were consistent with a thyroid carcinoma that produced an excess of thyroid hormone. It should be admitted, however, that a diagnosis of malignant lymphoma was more likely on clinical grounds. The urinary excretion of I^{131} and the PBI indicated that the patient was in a euthyroid state. Later a lymph node biopsy proved the diagnosis of Hodgkin's disease.

An interesting diagnostic problem was presented by the following patient:

Case 251. A 31-year-old man complained chiefly of shortness of breath of one year's duration. A cough which he had had intermittently for several years became productive. He had lost seven kg. in four months. His appetite was poor. He was not intolerant to heat but perspired at night. He became weak and easily fatigued. Occasionally he was bothered with palpitation. He had noted swelling of his neck for several years. His eyes had always been somewhat prominent.

The physical examination revealed a rather poorly nourished man. The skin was warm but not moist. The thyroid was about 2 × normal size. It was smooth and moderately firm. The eyes were slightly prominent with wide palpebral fissures and lid lag. Pulse was regular at a rate of 120. There was flatness and absent breath sounds in the left chest below the third rib anteriorly and the forth rib posteriorly. X-rays of the lungs showed a left hydrothorax. The situation in the underlying lung could not be determined.

The WBC was 5,200 with 31 per cent lymphocytes and 8 per cent monocytes. BMR's were not obtained because of the possibility of tuberculosis. PBI's were 7.6 and 4.7 μg. per cent. The 48-hour excretion of I^{131} was 61.7 per cent.

About one month later a small, firm nodule was observed in the left supraclavicular fossa. A biopsy gave the diagnosis of lymphoblastoma. The patient died three months later. The tumor involved lymph nodes, lung, liver, spleen, and bone marrow. The thyroid showed a nontoxic goiter.

Remarks:—The history of goiter, prominent eyes, weight loss, palpitation, and sweating were suggestive of thyrotoxicosis. The physical findings except for the pleural effusion were consistent with thyrotoxicosis. There was the possibility of thyrotoxicosis in addition to the disease that caused his pulmonary pathology. The normal excretion of I^{131} indicated a euthyroid state. The subsequent course proved that the test had been correct.

The results show that the radioactive iodine tolerance test may be used as an aid in excluding thyrotoxicosis in patients with diseases of the blood and reticuloendothelial system.

6. Nonthyrotoxic Goiters

The diagnosis of thyrotoxicosis had also to be excluded in patients with euthyroid goiters (nontoxic goiter, carcinoma of the thyroid, and chronic thyroiditis) in whom accompanying symptoms and signs or elevated basal metabolic rates to some extent suggested thyrotoxicosis.

Eleven patients presented such problems (Cases 253—259, 284, 288, 295, and 305). The final diagnoses were nontoxic goiter (7 cases), carcinoma of the thyroid (2 cases), and chronic thyroiditis (2 cases). Two patients (Cases 382 and 383) who did not have goiters will also be discussed in this group because of the similarity of the diagnostic problems that they presented. The clinical and laboratory data are presented in Table 40 and Table 41 (Cases 382 and 383).

In some patients a marked loss of weight combined with the presence of goiter (Cases 253, 254, and 255) or weight loss, palpitation, and nervousness (Case 382) raised the possibility of thyrotoxicosis. It should be admitted that the suspicion of thyrotoxicosis was rather remote and that it could be ruled out clinically. The normal excretion of radioactive iodine and the normal serum protein-bound iodine (determined in two patients) served as confirmation of the clinical impression. It may be observed that in Case 254 the urinary excretion of I^{131} was normal in spite of the presence of a large colloid goiter (120 grams removed at operation).

The question of differential diagnosis was somewhat more complicated in Cases 256—259 (Table 40). The history of weight loss (Cases 257 and 258), nervousness (Cases 256, 258, and 259), sweating (Cases 258 and 259), and other symptoms in association with goiter, tachycardia (Cases 257 and 259), and elevated basal metabolic rate (Cases 256 and 258) suggested thyrotoxicosis. The normal urinary

Table 40. **Clinical and laboratory data in patients with**

Case number	Age Sex	History										Physical					
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes		
															Exophthalmos	Lid lag	Lid retraction
253	33 ♀	+	0	0	0	0	0	0	0	0	0	1½, D, s	c, m	+	0	0	0
254	53 ♂	+	0	0	0	0	0	+	0	0	0	5, D, f	n	0	0	0	0
255	54 ♀	+	0	0	0	+	0	+	0	0	0	2, N, f	w, d	0	0	0	0
256	60 ♀	0	0	0	0	0	0	+	0	+	0	2, D, s	n	0	0	0	0
257	30 ♀	+	0	0	0	0	0	+	0	0	0	1½, D, f	n	0	0	0	0
258	32 ♀	+	0	0	+	0	0	+	0	+	0	5, D, f	w	0	0	0	0
259	17 ♀	0	+	+	+	+	0	+	0	+	0	1½, N, s	c, m	0	0	0	0
284	58 ♀	+	0	0	0	+	+	+	0	0	0	2½, D, f	d	0	0	0	0
288	32 ♀	+	0	0	+	+	0	+	0	+	0	3, N, f	n	0	0	0	0
295	69 ♂	0	0	0	0	0	0	+	0	0	0	2, D, f	n	0	0	0	0
305	62 ♀	+	0	0	0	0	0	+	0	+	0	3, D, h	n	0	0	0	0

excretion of I^{131} and the normal serum protein-bound iodine indicated a euthyroid state. This was further supported by the findings at operation of a nontoxic nodular goiter (mainly colloid adenoma, Case 258) and an adenoma with a hemorrhagic cyst (Case 259). Cases 256 and 257 did not develop thyrotoxicosis during the period of observation (3 and 12 months, respectively).

Thyroid carcinoma may cause thyrotoxicosis in rare cases. It was necessary to consider this possibility in Cases 284 and 288 (Table 40). The history of weight loss, fatigue, sweating (Case 288), palpitation (Case 284), and nervousness (Case 288) in combination with goiter, tachycardia, and elevated basal metabolic rate was consistent with thyrotoxicosis. The urinary excretion of I^{131} and the PBI did not indicate thyrotoxicosis. It should be admitted that the diagnosis of thyroid carcinoma was established before these tests were done. The further clinical course definitely established that thyrotoxicosis was not present.

Case 383 (Table 41) presented a similar diagnostic problem although thyrotoxicosis was not seriously suspected. He had lost considerable weight and was found to have a large mass in the mid-mediastinum. The question of hyperfunctioning thyroid adenoma was raised. The normal excretion of I^{131} and the normal PBI demonstrated a euthyroid state. Direct measurements with a Geiger-Müller counter over the chest indicated that no I^{131} was taken up by the mass. Later a biopsy gave the diagnosis of carcinoma of the lung.

Although the disturbance of thyroid function which accompanies chronic thyro

nonthyrotoxic goiter without extrathyroidal disease.

Examination					Laboratory findings						Diagnosis
Heart								Urinary excretion of I^{131} in per cent			
Enlargement	Fibrillation	Pulse rate	Blood pressure	Edema	Cholesterol mg per cent	BMR per cent	PBI µg per cent	0—24 hours	24—48 hours	Total in 48 hours	
0	0	90	135/85	0		+ 9		54.5	3.0	57.5	Nontoxic goiter.
0	0	76	100/60	0	236	— 2		47.3	6.4	53.7	» »
0	0	88		0		—12	3.1	54.5	0.6	55.1	» »
0	0	62	155/90	0		+23	3.8	43.2	14.5	57.7	» »
0	0	100	125/80	0	160	+17	4.4	49.3	0.5	49.8	» »
+	0	84	155/90	0	390	+29	6.2	50.9	2.8	53.7	» »
0	0	96	100/65	0		— 7	6.3	61.4	2.3	63.7	» »
+	0	110	130/50	+	170	+23	5.5	45.5	8.1	53.6	Carcinoma of the thyroid.
0	0	120	120/65	0	98	+41	4.8	69.4	3.6	73.0	» » » »
0	0	96	180/90	0		+26	4.7	69.3	14.8	84.1	Chronic thyroiditis.
+	0	84	145/80	0	160	+21	4.0	55.8	7.4	63.2	» »

iditis is usually hypothyroidism, there are patients in whom there is a possibility of hyperthyroidism. Two such patients (Cases 295 and 305, Table 40) were studied. The question of thyrotoxicosis was raised particularly by the elevated basal metabolic rate. The 48-hour excretion of I^{131} was normal, but the 24—48 hour excretion in Case 295 was higher than normal and consistent with the findings in myxedema. The PBI was normal. Thus, the laboratory tests indicated that thyrotoxicosis was not present. The findings at operation of chronic thyroiditis confirmed the results of the tests.

The results demonstrate that the radioactive iodine tolerance test is of value in excluding thyrotoxicosis in patients with euthyroid goiters that are associated with symptoms and signs imitating thyrotoxicosis.

7. Miscellaneous Diseases

The question of thyrotoxicosis has to be considered in a variety of other nonthyroid diseases. The disease in itself may give symptoms and signs which simulate thyrotoxicosis or the disease may prevent the clinical evaluation of the functional state of the thyroid. Differential diagnostic problems arise particularly if a goiter is also present or the BMR is elevated.

Twelve patients presenting such problems were studied (Cases 260—267 and 382—385). The clinical and laboratory data are summarized in Table 41. For practical

Table 41. Clinical and laboratory data in patients w

Case number	Age Sex	History										Phys				
		Weight loss	Increased appetite	Intolerance to heat	Sweating	Fatigue	Palpitation	Swelling of the neck	Prominence of the eyes	Nervousness	Tremor	Thyroid size and type	Skin	Tremor	Eyes		
															Exophthalmos	Lid lag	Lid retraction
382	24 ♀	+	0	0	0	0	+	0	0	+	0	1, D, s	n	0	0	0	0
383	47 ♂	+	0	0	0	0	0	0	0	0	0	1, D, s	m	0	0	0	0
260	23 ♀	0	0	0	0	+	0	+	0	+	0	2½, D, s	n	0	0	0	0
261	47 ♀	+	0	+	0	+	+	0	0	+	0	2, N, f	n	0	0	0	0
262	48 ♀	+	0	0	0	0	+	0	0	+	0	2, D, f	n	0	0	0	0
263	72 ♀	+	0	+	0	0	+	+	0	+	0	1½, N, f	w, m	0	0	0	0
384	17 ♀	+	+	0	0	+	+	+	0	+	0	1, D, f	c, m	+	0	0	0
264	51 ♂	0	0	0	0	0	+	+	0	+	0	1½—2, N, s	n	+	0	0	0
265	57 ♀	0	0	+	0	+	+	0	+	+	0	2, N, f	n	0	0	0	0
266	65 ♀	+	0	0	0	0	+	+	0	+	0	5—6, N, f	n	0	0	0	0
267	40 ♀	+	0	0	0	0	+	0	0	+	0	2, N, f	w, m	+	0	0	0
385	17 ♀	+	0	0	+	+	0	0	0	+	0	Not palpable	c, m	+	0	0	+

reasons Cases 382 and 383 were discussed together with patients with nonthyrotoxic goiters and are not included in the following presentation.

The possibility of thyrotoxicosis was raised because of rather suggestive histories with weight loss (7 cases), intolerance to heat (3 cases), palpitation (8 cases), and nervousness (10 cases). These histories appeared in patients with goiter (8 cases), warm and moist skin (2 cases), tachycardia (3 cases), and elevated basal metabolic rates (6 cases). It can be said at once that thyrotoxicosis was easily excluded clinically in Cases 260, 261, and 262, and the normal excretion of I^{131} served to confirm the clinical diagnosis.

The diagnostic difficulties presented by the remaining seven patients may best be indicated by two case reports.

Case 263. This 72-year-old woman was hospitalized because of fracture of the neck of her right femur. It was observed that she had a nodule in her thyroid. The lump had been present for 15 years. She had always been nervous and intolerant to heat. She had lost about 12 kg. in weight the last year. The examination showed a 2×2 cm. firm nodule in the right lobe and at least one smaller nodule in the left lobe of her thyroid. There were no signs of thyrotoxicosis. BMR was +3 per cent. PBI was 4.0 μg. per cent. The 48-hour excretion of I^{131} was 53.9 per cent. About one year later she was hospitalized again with a diagnosis of rheumatoid arthritis. In the interval she had lost seven kg. in weight and had felt more nervous.

The examination showed a quiet, thin woman. The skin was warm and moist. The thyroid status had not changed from the earlier examination. Pulse rate was 85—90.

BMR's were +31 and +44 per cent. PBI was 3.4 μg. per cent. The 48-hour excretion of I^{131}

cellaneous diseases simulating thyrotoxicosis.

ination				Laboratory findings						
eart							Urinary excretion of I^{131} in per cent			Diagnosis
Fibrillation	Pulse rate	Blood pressure	Edema	Cholesterol mg per cent	BMR per cent	PBI μg per cent	0—24 hours	24—48 hours	Total in 48 hours	
0	60	110/70	0		— 1	4.6	63.6	3.6	67.2	Weight loss of undetermined origin.
0	88	110/65	0	163	+10	4.6	58.0	5.3	63.3	Carcinoma of the lung.
0	80	120/70	0	245	— 8	5.2	54.7	1.2	55.9	Myasthenia gravis + Nontoxic goiter.
0	84	140/80	0		— 5	6.4	64.6	3.4	68.0	Bronchial asthma + Nontoxic goiter.
0	80	135/70	0		± 0		79.7	4.4	84.1	Menopause + Nontoxic goiter.
0	86	155/85	0		+38	3.4	55.8	10.0	65.8	Rheumatoid arthritis + Nontoxic goiter.
0	132	125/80	0		+23	5.5	54.0	1.6	55.6	Epilepsy.
0	78	150/100	0		+49	3.9	57.6	6.5	64.1	Chronic alcoholism + Nontoxic goiter.
0	80	140/80	0		+27	6.3	58.7	7.7	66.4	Bronchial asthma + Nontoxic goiter.
0	80	120/80	0	169	+16	11.7	65.8	3.1	68.9	Chronic cholecystitis + Nontoxic goiter.
0	100	140/90	0	278	+25	9.2	58.8	6.1	64.9	Sarcoidosis + Nontoxic goiter.
0	120	175/115	0	180	+65	4.8	24.5	15.2	39.7	Pheochromocytoma + Renal impairment.

was 65.8 per cent. Two months later, when her rheumatoid arthritis had improved considerably, the BMR was +1 per cent.

Remarks: At the first examination there was little doubt that the patient was in a euthyroid state. On the second occasion her continued weight loss and increased nervousness in association with nodular goiter made it necessary to consider the diagnosis of thyrotoxicosis. The clinical findings were not characteristic of thyrotoxicosis, but the elevated BMR was confusing, particularly since the BMR had been normal one year previously. The normal excretion of I^{131} and the normal PBI aided in ruling out thyrotoxicosis. More emphasis than usual could be placed on these tests because of the studies made one year previously. The subsequent course proved that the tests had been correct. It should be observed that the BMR became normal when her rheumatoid arthritis improved.

Case 384. A 17-year-old girl was studied with the chief complaint of tiredness of one year's duration. She had lost four kg. in weight in spite of a good appetite. For about a year she had been bothered with palpitation even while at rest. She had felt nervous and emotionally unstable. About one year previously she had had four attacks of generalized convulsions with loss of consciousness and biting of the tongue.

The physical examination was negative except for cool and moist skin, a fine tremor of the fingers, and a pulse rate of 132. Neurological examination was negative.

BMR's were +22, +7, +26, and +37 per cent. PBI's were 5.3 and 5.7 μg. per cent. The 48-hour excretion of I^{131} was 55.6 per cent.

Remarks:—It was likely that this patient had epilepsy, a diagnosis that later became well established. The problem was to determine if thyrotoxicosis was present in addition. The history of weight loss despite good appetite, palpitation, nervousness, and emotional instability was suggestive. When she received treatment for her epilepsy the BMR returned to normal, and there was no further evidence of thyrotoxicosis. The I^{131}-excretion and the PBI had indicated the correct state of thyroid function.

The elevated BMR in Case 264 was probably caused by restlessness (chronic alcoholism). Six months later the BMR was +2 per cent and a nontoxic nodular goiter was found at operation. In Case 265 the elevated BMR was probably due to bronchial asthma.

In Case 266 the diagnostic situation was confusing. The history was consistent with thyrotoxicosis although it was not characteristic. The physical examination failed to demonstrate thyrotoxicosis, but a large goiter was present. The BMR was normal as was the urinary excretion of I^{131}, while the PBI was elevated. A diagnostic test with potassium iodide was negative. At operation a large nontoxic nodular goiter was found. This finding indicated that the radioactive iodine tolerance test had been correct. No explanation for the elevated PBI was found.

Case 267 presented an interesting diagnostic problem. Her history and clinical picture were compatible with thyrotoxicosis. The first PBI was elevated while the urinary excretion of I^{131} was normal. She was found to have sarcoidosis involving the lungs and the skin. Whether the disease also involved the thyroid cannot be stated. After prolonged clinical observation (10 months) and repeated radioactive iodine tolerance tests and serum protein-bound iodine analyses, which all gave normal values with the exception of the first PBI, thyrotoxicosis was excluded. The elevated PBI in the first test was probably due to an analytical error.

Case 385 presented an unusual diagnostic problem. Although the history and clinical picture were not characteristic of thyrotoxicosis, they were suggestive enough for it to be considered. Her chief complaints were weakness and nervousness. She was found to have cardiac enlargement, tachycardia, and a basal metabolic rate of +65 per cent. The PBI was normal. The 48-hour urinary excretion of I^{131} was 39.7 per cent and was thus in the thyrotoxic range. However, the excretion pattern showed that the low total excretion was not due to thyroid hyperfunction. The excretion of 15.2 per cent during the 24—48 hour period was compatible either with impaired renal function or hypothyroidism. The urea clearance of 29 per cent of the normal explained the observed excretion of I^{131}.

The PBI, determined in nine patients, was normal in seven cases and elevated in two cases. The elevated values have already been dicussed.

The results of the radioactive iodine tolerance test show that it may be possible to use this test in excluding thyrotoxicosis in patients in whom an extrathyroid disease obscures the clinical evaluation of the state of thyroid function. The test is of particular value when the basal metabolic rate is elevated on some other basis than hyperthyroidism.

Discussion

The evaluation of the radioactive iodine tolerance test in the differential diagnosis of thyrotoxicosis is based on studies of 84 patients with a variety of diseases. Actually, thyrotoxicosis was not seriously suspected in all patients, and the diagnosis of thyrotoxicosis could be ruled out clinically in some of the patients even at the time of study. The review of this group of patients has clearly indicated that a large number presented problems in differential diagnosis at the time of study.

In evaluating a diagnostic procedure the means by which the diagnosis is established is of fundamental methodological importance. There may often be a suspicion that the results of the test have influenced the diagnosis. This is of particular danger if the person developing a test is also responsible for making the diagnosis. This difficulty has been minimized in the present study, inasmuch as the clinical diagnoses were not made by the author. In most instances the final diagnosis represented the consensus of opinion of several clinicians, including specialists in particular fields where indicated. Furthermore, in a number of cases a histological diagnosis of thyroid tissue was available. In other situations it was possible to rule out thyrotoxicosis when suggestive symptoms disappeared during specific treatment for other diseases. In doubtful cases the final diagnosis was made on the basis of an extended follow-up.

There are certain situations in which these various diseases may be readily confused with thyrotoxicosis. The clinical picture may be indistinguishable from that of classic thyrotoxicosis as in thyrotoxicosis factitia. On other occasions certain findings in patients with cardiovascular disease and anxiety neurosis are suggestive of atypical thyrotoxicosis. Furthermore, in any constitutional illness the finding of a goiter or an elevated BMR or both makes thyrotoxicosis a conspicuous possibility.

In the present group of 84 patients with diseases that may simulate thyrotoxicosis the radioactive iodine tolerance test in no case indicated thyrotoxicosis. It is true that in one patient (Case 385) the total 48-hour excretion of I^{131} was less than normal. However, the relative proportions of the 0—24 and 24—48 hour excretion indicated that the low excretion was not due to thyroid hyperfunction.

The serum protein-bound iodine, determined in 59 patients, gave incongruously elevated values in three patients. Furthermore, the elevated serum protein-bound iodine values in the three patients with thyrotoxicosis factitia were misleading from a diagnostic point of view, although they did demonstrate the actual level of circulating thyroid hormone.

The results of the radioactive iodine tolerance test show that it is a reliable test in the differential diagnosis of thyrotoxicosis. Its high degree of specificity is indicated by the fact that the urinary excretion of I^{131} does not suggest thyroid hyperfunction in spite of symptoms and signs that may be mistaken for thyrotoxicosis.

There are a few situations, however, in which the results of the radioactive iodine tolerance test must be interpreted with care. These are not common or of any considerable importance. They have already been dealt with in Chapter VII, but they will be discussed briefly here from the point of view of clinical use.

Before proceeding with the test in an individual patient it must be determined if he has had any recent X-ray of the gall bladder, kidneys, or any other organ involving the use of contrast media containing iodine. Any such administration of iodine compounds will result in an increased excretion of I^{131}. In practice, however, the only important source is gall bladder dye. Lipiodol is given only rarely, and dyes administered for intravenous pyelograms will have an effect for only a few days, while the gall bladder dye may increase the excretion of I^{131} over a period of several months or perhaps even more. In the present study four thyrotoxic patients (Cases 96, 101, 135, and 170) were observed in whom previous cholecystograms apparently increased the excretion of I^{131}. In one patient the I^{131}-excretion was still less than normal though higher than usually observed in thyrotoxicosis, and in two patients the excretion was in the low normal range, between $-2\,\sigma$ and $-3\,\sigma$ of the normal mean. Therefore, whenever a patient who has had a recent cholecystogram gives values in this range, it is likely that he has thyrotoxicosis.

It is also important to remember that the PBI is falsely elevated after the administration of gall bladder dye. Consequently, the increased values, which, for instance, were found in those patients referred to above, could not be regarded as evidence for thyrotoxicosis. Thus, following a cholecystogram the I^{131}-test (but not the PBI) may be of help in establishing the diagnosis of thyrotoxicosis, and conversely, the PBI (but not the I^{131}-test) may assist in excluding thyrotoxicosis.

Before interpreting the results of the radioactive iodine tolerance test it is necessary to know whether the patient recently has received medicinal iodine in any other form, as it may also increase the excretion of I^{131}. Following the discontinuation of iodine medication, a normal excretion of I^{131} cannot be used to exclude thyrotoxicosis for a period of about two weeks.

The same precautions should be taken regarding antithyroid drugs. Following the omission of such drugs after prolonged use, the thyroid may go through a short period of increased avidity for iodine during which a low excretion of I^{131} does not indicate thyrotoxicosis. To be safe, it is probably better to wait for about two weeks after discontinuing iodine or antithyroid drugs before using the radioactive iodine tolerance test.

As for the PBI, this test may be used even during the administration of iodine or antithyroid drugs, although the changes in the PBI and the clinical picture do not run parallel during the course of treatment.

Another principal factor to be considered is the status of renal function. In the presence of renal impairment the urinary excretion of I^{131} may be delayed, and the total 48-hour excretion may be less than normal. In a number of patients with renal damage it is possible to tell from the relative proportions of the excretion of

I^{131} for the 0—24 and 24—48 hour intervals that a low total excretion is not due to thyroid hyperfunction. However, there are patients with renal failure in whom it is not possible to determine from the ordinary radioactive iodine tolerance test whether thyroid hyperfunction or renal failure or both are present. In such situations a more complicated procedure of determining the excretion rate may be advantageous. The combination of thyrotoxicosis (or diseases simulating thyrotoxicosis) and renal impairment is rare, however. In hypertensive cardiovascular disease the urinary excretion of I^{131} was not below normal in any patient.

In conclusion, it can be said that from the clinical standpoint the factors that may influence the radioactive iodine tolerance test are rather unimportant, as they are easily recognized. Therefore, these factors do not appreciably detract from the value of the radioactive iodine tolerance test as a diagnostic aid.

Chapter X

THE COLLECTION OF RADIOACTIVE IODINE BY THE THYROID

Although it has been clearly demonstrated that the radioactive iodine excretion test is a valuable method for the diagnosis of disturbances in thyroid function, it involves certain inconveniences. It is relatively simple as far as the actual determination of radioactivity in the urine is concerned. However, the prolonged collection of complete urine specimens is not only troublesome for patients and personnel, but there is a considerable chance for inaccuracy if the collections are not carefully supervised. There is also the theoretical objection that the urinary excretion of I^{131} is only an indirect measure of the thyroid's avidity for iodine.

It would simplify the radioactive iodine tolerance test if the amount of I^{131} collected by the thyroid could be determined directly. The gamma radiation from I^{131} is penetrating enough to be detected over the thyroid. Methods for direct measurements, or "*in vivo*" measurements as they are generally called, have been suggested by several investigators as discussed in Chapter II. In the present study an attempt has been made to develop a more accurate method for the determination of the amount of I^{131} collected by the thyroid following the oral administration of a tracer dose of I^{131}.

The basic reason for the majority of inaccuracies in all *in vivo* measurements of radioactivity in the thyroid is the uncontrollable geometrical arrangement of the source of radiation. The Geiger-Müller counter cannot be placed in exactly the same position relative to the thyroid in different patients because of variations in size and anatomical location of the thyroid. Thus, there will be variations not only in the distance between the source and the detector but also in the size of the source. The absorption and scattering of the gamma rays in the thyroid and overlying tissues are also subject to individual variation. It is impossible to arrange a standard container for the I^{131} having exactly the geometry of the thyroid. Any sort of "phantom" used to duplicate the geometry in the neck must give rise to considerable error through ignorance of actual conditions. The inability to evaluate all factors that influence the *in vivo* measurements of I^{131} does not mean that such measurements cannot be used to advantage. It is important, however, to be aware of the fallacies and limitations of the *in vivo* measurement technique when it is employed quantita-

tively. The accuracy of *in vivo* measurements of I^{131} is, of course, much less than the accuracy of analyses of radioactive iodine in the urine.

Differences in size and location of the thyroid gland will become increasingly less important when the detecting instrument can be placed at a greater distance from the gland. It was hoped, therefore, that the measurements could be made with the Geiger-Müller tube placed at a considerable distance from the gland. Preliminary experiments demonstrated that the regular bell type solid-cathode Geiger-Müller counter was not sufficiently sensitive to the gamma rays of I^{131}. It was also probable that with a counter of this type the variations in the geometry of the neck were influencing the results even more than necessary. A cylindrical counter occupying a larger solid angle was found to be more accurate. It was also taken into account that the sensitivity to gamma rays is increased by employing screen instead of solid cathodes (Evans and Mugele, 1936). It was observed that a counter with an 80-mesh screen cathode (i. e., having 80 wires in each direction per square inch) had about twice the efficiency for I^{131} of a counter with the same dimensions where the cathode was solid. Evans and Mugele (1936) also demonstrated that with an increasing atomic number of the cathode material the sensitivity of the counter increased. For the *in vivo* measurements a copper cathode counter (atomic number = 29) was chosen. Higher sensitivity would have been obtained by using a cathode of platinum (atomic number = 78), for example, as was employed for the standardization of I^{131}, but such counters were not available.

Procedure of the test

1. A tracer dose of I^{131} was prepared and administered as described on page 38.
2. The uptake of I^{131} by the thyroid was measured 48 hours after the administration of the tracer dose.
3. For each test an identical dose of I^{131} was made up in a volumetric flask and saved as a standard. The standards were always placed in identical flasks in order to insure constant geometrical relations for the reference source.

Apparatus and method of measurement

Geiger-Müller Counter. The detector was identical with that described on page 32 except for the cathode which was an 80-mesh copper screen. Peacock (1944) demonstrated that gamma ray counters of this construction could be duplicated with the same absolute efficiency. Three counting tubes used in this investigation did not differ in their sensitivity to I^{131} more than 3—5 per cent.

The counter was mounted on an X-ray stand as seen in Fig. 18 so that it could be placed in any desired position in regard to the thyroid.

Recording device. The impulses from the counter were fed through a preamplifier of the standard Neher-Pickering type to a scaling circuit.

The arrangements for making the measurements are shown in Fig. 18. The patient was placed flat on the bed. The isthmus of the thyroid gland was palpated

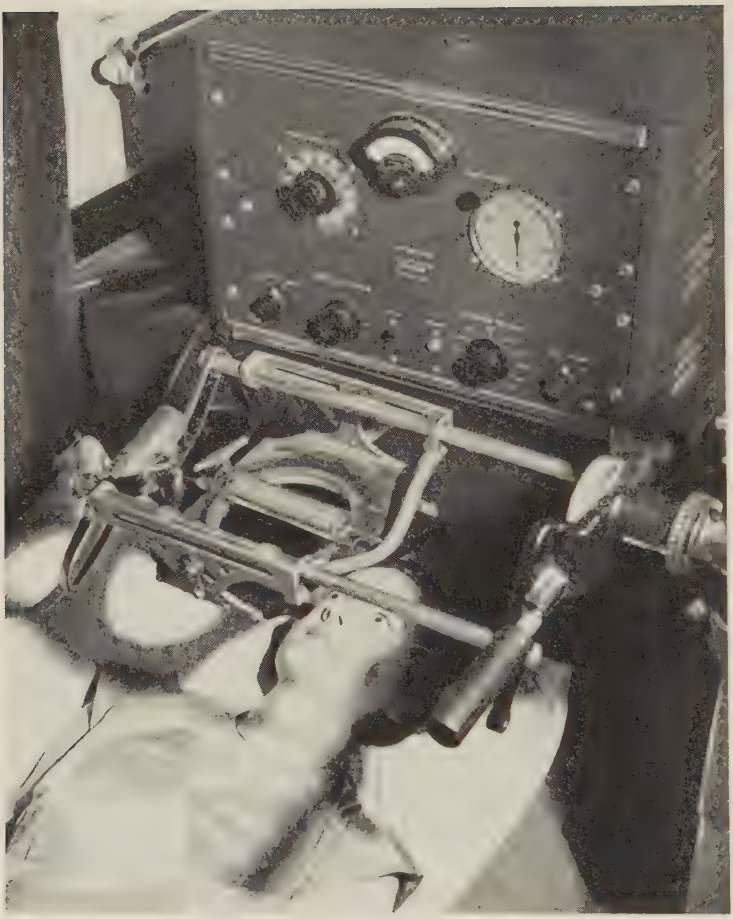

Fig. 18. The arrangement used for the direct measurement of the uptake of I^{131} by the thyroid.

and marked. The counter was centered over the isthmus of the thyroid at a distance of 40 cm. This position was chosen as the counting rate was reasonably high in most cases even at such a long distance, and at a shorter distance, such as 20 cm., the results correlated less well with the urinary excretion data. As the distance is increased, differences in size, shape, and anatomical location of the thyroid are minimized. Duplicate readings were taken. By subtracting the background the net counting rate was obtained. It was expressed as counts per minute (CPM). This counting rate was then compared with that of the standard.

In order to express the counting rate obtained over the thyroid directly in per cent of the administered dose of I^{131} it would be necessary to measure the standard in a geometrical arrangement identical with that of the thyroid. Attempts in that

direction have been made by QUIMBY and MCCUNE (1947) and others who prepared "phantom" thyroids in which the I^{131} was enclosed. It seemed to the present writer that it would be quite impossible to make such identical arrangements. Therefore, the standard was measured in an arbitrarily selected but absolutely constant geometry. The standard was always prepared in identical 100 ml. volumetric flasks. The counting rate of the standard was measured at a distance of 30 cm. from the Geiger-Müller tube. The relative position is unimportant as long as it is constant. Under no circumstances will the thyroid and the standard have the same geometry relative to the counting tube. The ratio of $\frac{CPM_{patient}}{CPM_{standard}}$ then expresses in an arbitrary way the amount of I^{131} taken up by the thyroid. This arbitrary ratio can be used as an index of the uptake of I^{131} by the thyroid, and it would be possible to compare the uptake of I^{131} by the thyroid in normal and diseased subjects on the basis of this ratio. However, for practical reasons it is more convenient to express the collected I^{131} in per cent of the administered dose. This conversion of the arbitrary ratio to a percentage of the administered dose is done by means of a conversion factor. This conversion involves the use of the urinary excretion data. The difference between the administered dose and the amount of I^{131} excreted in the urine represents the amount of I^{131} retained in the body. If practically all of the excretion of I^{131} is completed in the collection period of 48 hours, and if all of the retained I^{131} is present in the thyroid, then the amount retained (as determined from the urinary excretion) may be directly compared with the amount found in the thyroid by the *in vivo* measurements.

That the urinary excretion of a tracer dose of I^{131} is almost completed in 48 hours in euthyroid and hyperthyroid subjects is indicated by such data as the excretion curves published by KEATING *et al.* (1947). From the practical point of view the excretion of I^{131} that takes place after the 48-hour interval may be neglected.

Furthermore, it is reasonable to assume that substantially all the I^{131} administered as a tracer dose is either collected by the thyroid or excreted in the urine. The validity of this assumption is supported by the fact that the 48-hour excretion of I^{131} varied between 93.3 and 98.4 per cent in eight totally thyroidectomized patients. (Table 14, p. 54.)

The comparison between the two sets of retention values was carried out as indicated in Table 42. For each patient an individual conversion factor was calculated. Such factors were determined in 136[1] euthyroid and hyperthyroid subjects. Hypothyroid patients were not included since the amount of I^{131} in their thyroids is usually too small to permit accurate measurements. Furthermore, in hypothyroid subjects the excretion of I^{131} is often not completed in 48 hours. Patients with renal impairment were also excluded as the excretion of I^{131} may be delayed in such diseases (see Fig. 17, p. 97).

From all the individual factors an average conversion factor was obtained. For

[1] Seven of the patients were used only for the *in vivo* measurements.

Table *42*. Conversion of *in vivo* measurement data into percentage of the administered dose of I^{131}.

Case number	Direct measurement over thyroid $\frac{CPM\text{patient}}{CPM\text{standard}} = A$	Uptake of I^{131} by thyroid calculated from urinary excretion $= A_1$ (per cent)	Conversion factor $= \frac{A_1}{A \times 100}$	Thyroid size
68	$\frac{631}{1006} = 0.627$	84.2	1.34	$1\frac{1}{2}$
69	$\frac{697}{1010} = 0.690$	87.6	1.27	2—3
58	$\frac{716}{1090} = 0.657$	85.8	1.31	2—3
240	$\frac{205}{1224} = 0.167$	23.6	1.41	$2\frac{1}{2}$—3
26	$\frac{484}{1224} = 0.395$	62.9	1.59	2
149	$\frac{539}{1224} = 0.440$	58.7	1.33	$1\frac{1}{2}$
383	$\frac{288}{1146} = 0.251$	36.7	1.46	1
87	$\frac{692}{1171} = 0.591$	91.0	1.54	3
172	$\frac{651}{1149} = 0.567$	72.3	1.28	2
330	$\frac{302}{990} = 0.305$	50.0	1.64	2

the total number of 136 patients this factor was found to be 1.49 ± 0.01 with a standard deviation of ± 0.17. It should be stressed that the conversion factor does not have any general significance. It is only valid for the measurement set-up used in the present study. For any variation from the present arrangement the factor will be different and has to be determined experimentally.

By multiplying the ratio of $\frac{\text{CPM}_{\text{patient}}}{\text{CPM}_{\text{standard}}}$ by this conversion factor (and multiplying by 100) the percentage uptake of I^{131} by the thyroid is obtained.

From Table 42, which includes the first patients for whom conversion factors were calculated, it can be seen that the standard does not give the same number of counts in each patient. This is caused by inaccuracies in the standardization of I^{131}, inaccuracies in the correction for decay, inaccuracies in the measurements, and so forth. It should be emphasized that the ratio of $\frac{\text{CPM}_{\text{patient}}}{\text{CPM}_{\text{standard}}}$ will not be affected by such variations in the size of the administered dose of I^{131}.

In order to determine whether the presence of goiter affected the results of the *in vivo* measurements the present group of 136 patients were divided into two groups: patients without goiter and patients with goiter. The size of the goiters varied from $1\,{}^{1}/_{2}$ to 8 times normal size as judged by palpation. In the 36 patients without goiter the conversion factor was 1.48 ± 0.03 and in the 100 patients with goiter the factor was 1.50 ± 0.02. This result indicates that the presence of goiter had no effect on the *in vivo* measurements in the present study. This is probably explained by the fact that the measurements were made at a considerable distance (40 cm.) from the thyroid. There was no apparent correlation between the size of the goiter and the conversion factor.

It should be emphasized that this conversion factor is correct only on the assumption that the thyroid collects all the I^{131} that is not excreted in the urine. It does not take into account either the amount of I^{131} excreted by routes other than the kidneys or the I^{131} distributed in other parts of the body. However, the urinary excretion of I^{131} in the totally thyroidectomized patients indicated that these fractions were small. This is also supported by the fact that in three patients with thyrotoxicosis factitia the 48-hour excretion of I^{131} was 94, 97, and 98 per cent, respectively. The uptake of I^{131} by the thyroid as calculated from the urinary excretion data is probably slightly too high, but it seemed reasonable to disregard this error on the basis of the above observations. Furthermore, such an error will not affect the comparison between euthyroid and hyperthyroid patients.

The relation of the uptake of I^{131} by the thyroid determined directly from *in vivo* measurements and indirectly from urinary excretion data is presented in Fig. 19. The coefficient of correlation was found to be $+0.97 \pm 0.06$. The fact that a conversion factor has been used does not affect the correlation. The very high correlation suggests that it may be possible to use direct measurements of the uptake of I^{131} by the thyroid as a diagnostic test instead of the urinary excretion test. However, the diagnostic value of the *in vivo* measurements cannot be determined finally from the present study. It was not possible to make studies of the uptake of I^{131} in normal subjects because of the safety regulations at the Massachusetts General Hospital which limit the amount of I^{131} given to normal subjects to 10 μc. or less. At least 50 μc. doses of I^{131} would have been required to obtain satisfactory *in vivo* measurements with the equipment employed. Therefore it was necessary to use a group of euthyroid patients as controls for the estimation of the diagnostic value of the *in vivo* measurement method.

The total number of patients on whom *in vivo* measurements were obtained was 136. There were 53 euthyroid patients and 71 hyperthyroid patients. In addition, there were 12 patients who received treatment affecting thyroid function at the time of study. These latter patients were used in the calculation of the conversion factor but not for the present purpose. Forty-three of the hyperthyroid patients had clinically apparent thyrotoxicosis, while the remaining 28 patients belonged to the group previously referred to as thyrotoxicosis with diagnostic problems. It is true that

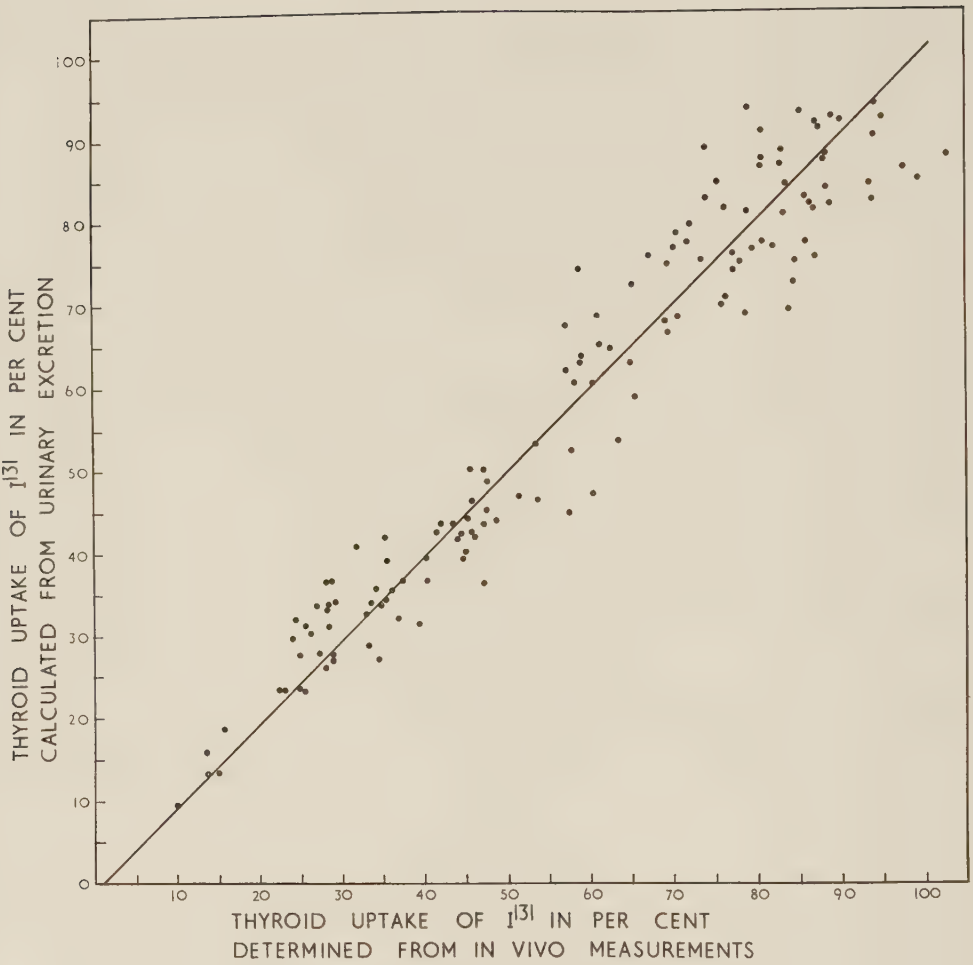

Fig. 19. The relation of the direct determination of the uptake of I^{131} by the thyroid to the indirect determination calculated from the urinary excretion.

the group of euthyroid patients represents a rather heterogeneous group. However, the 48-hour urinary excretion of I^{131} in this group does not differ significantly from that of the normal (63.6 ± 1.1 per cent as compared with 65.9 ± 0.7 per cent for the normals). Furthermore, the standard deviation for the euthyroid controls of 7.8 agrees well with the normal value of 7.3. Therefore, it seemed justifiable to use the present group of euthyroid patients as controls for the comparison between the value of the urinary excretion test and the *in vivo* test as diagnostic aids in thyrotoxicosis. The results of this comparison are presented in Table 43. The average collection of I^{131} by the euthyroid patients was 37.5 ± 1.4 per cent with a standard deviation of 10.1. As the urinary excretion of I^{131} for this group of patients did not

Table 43. **Comparison between the results of the radioactive iodine tolerance test based on urinary excretion and on thyroid collection.**

Test	Euthyroid patients "Controls"			Hyperthyroid patients					
	Number	$M \pm \varepsilon (M)$ per cent	σ	Number	$< -3\sigma$	-3σ to $< -2\sigma$	-2σ to $+2\sigma$	$> +2\sigma$ to $+3\sigma$	$> +3\sigma$
48-hour urinary excretion of I^{131} ...	53	63.6 ± 1.1	7.8	71	68	2	1		
Uptake of I^{131} by the thyroid after 48 hours	53	37.5 ± 1.4	10.1	71			3	13	55

The standard deviations used in grouping the hyperthyroid patients are those of the euthyroid control group.

differ significantly from that of the normals, it is reasonable to assume that the thyroidal collection of I^{131} also should be fairly representative for normal conditions.

Table 43 presents the values for the 71 hyperthyroid patients distributed according to the standard deviations for the euthyroid control group both for urinary excretion and thyroid collection of I^{131}. It is apparent from the table that the urinary excretion of I^{131} is more sensitive in detecting thyroid hyperfunction than is the direct measurement of the uptake of I^{131}. While the urinary excretion of I^{131} was more than 3 σ below the mean of the euthyroid controls in 96 per cent of the thyrotoxic patients, the uptake of I^{131} was more than 3 σ above the mean of the controls in only 77 per cent. If the ± 2 σ limit is accepted as normal, the corresponding figures will be 99 and 96 per cent, respectively. The results show that there is more overlapping between euthyroid and thyrotoxic patients when the radioactive iodine tolerance test is based on the direct determination of the uptake of I^{131} by the thyroid. The overlapping is less, however, than that reported by Werner, Quimby, and Schmidt (1949) who presented the largest series so far studied.

The results indicate that the present *in vivo* measurement method to determine the total uptake of I^{131} by the thyroid is accurate enough to warrant its use for diagnostic purposes. Further studies are necessary to establish whether or not the *in vivo* determination can entirely replace the determination of the urinary excretion of I^{131}. It is probable that the loss in sensitivity, reliability, and accuracy will be balanced by the convenience of the *in vivo* measurement method.

Chapter XI

GENERAL DISCUSSION

The results of the different laboratory tests in patients with various states of thyroid function have been dealt with in detail for each disease entity. The usefulness of the radioactive iodine tolerance test in the diagnosis of thyrotoxicosis has been demonstrated. However, the results obtained with the radioactive iodine tolerance test as compared with other laboratory methods must be analyzed in further detail.

Table 44 summarizes the results of the basal metabolic rate, the serum protein-bound iodine, and the radioactive iodine excretion in the different diseases studied. The table is arranged so as to show the distribution of the tests in various diseases as compared with the normal variation for each test.

It may be questioned where the limits for the normal range should be placed. For the present study the $\pm 3\ \sigma$ limit was chosen so that a value lying outside this limit could be considered definitely abnormal. It is apparent that this is particularly advantageous for diagnostic purposes. Naturally due attention should be paid to the possibility that some values may be abnormal which fall within this range. This refers particularly to values in the zone between $2\ \sigma$ and $3\ \sigma$ from the normal mean. However, the table shows that a normal range based on the $\pm 3\ \sigma$ limit results in a better separation of euthyroid and hyperthyroid patients than does a normal range based on the $\pm 2\ \sigma$ limit. There are thus good reasons for using the $\pm 3\ \sigma$ limit for the normal range. This argument is valid if it is considered just as important to establish as to exclude the diagnosis of thyrotoxicosis. If it is more important that no case of thyrotoxicosis be missed, then the normal limit possibly should be placed at the $2\ \sigma$ limit even though it would mean that some euthyroid patients would erroneously be diagnosed as hyperthyroid.

It may be said at once that all the tests show characteristic differences among the groups of patients with hyperthyroidism, euthyroidism, and hypothyroidism. However, for diagnostic purposes it is also necessary to know the extent of overlapping of values between patients with normal and with disturbed function of the thyroid.

Table 44 clearly demonstrates that the BMR is not sufficiently sensitive and specific for the diagnosis of thyrotoxicosis. The BMR was found to be within normal

limits in a considerable number of patients with thyrotoxicosis. Furthermore, elevated basal metabolic rates were observed in a variety of other diseases than thyrotoxicosis. These results are in agreement with the observations of previous investigators as discussed in the review of the literature.

In the present study normal basal metabolic rates were observed in 22 per cent of thyrotoxic patients. This incidence cannot be considered characteristic of unselected thyrotoxicosis. The findings of Means (1948) that 12 per cent of women and 8 per cent of men had BMR's below +20 per cent in thyrotoxicosis are certainly more representative. The higher figure in the present study is due to the fact that patients with atypical and mild thyrotoxicosis were especially sought out so that the reliability of the different laboratory methods could be rigorously tested.

The elevated BMR's in patients without thyrotoxicosis appeared mainly in diseases previously known to raise the BMR. It should be noted that elevated BMR's may occur in carcinoma of the thyroid and in chronic thyroiditis in the absence of hyperthyroidism. The relatively large number of patients with nontoxic goiter and elevated BMR was due to the presence of goiters in patients with extrathyroidal diseases that in themselves may cause elevated BMR's. Decreased BMR's were observed not only in myxedema but occasionally in other patients without clinical hypothyroidism. It is possible that the low BMR in such patients is an indication of hypothyroidism that is not yet manifest clinically.

The results of the determination of the BMR demonstrate that the overlapping between euthyroid and hyperthyroid patients is too large to make this test a very reliable aid in the diagnosis of thyrotoxicosis.

The serum protein-bound iodine was observed to be elevated in 105 of 113 patients with thyrotoxicosis (93 per cent). This finding agrees well with those of previous investigators (Salter, Bassett, and Sappington, 1941; Riggs, 1947; Winkler, 1947). From the diagnostic point of view, however, it is more important that normal serum protein-bound iodine values were observed in eight of 56 thyrotoxic patients (14 per cent) in whom a clinical diagnosis of thyrotoxicosis could not be made with certainty at the time of study. The serum protein-bound iodine may be elevated very rarely in euthyroid patients as indicated in Table 44. These elevations are not related to any of the known factors that cause spurious elevations, such as cholecystograms or pyelograms, but may be due to analytical errors.

Nevertheless, the results demonstrate that the serum protein-bound iodine is a reliable and specific test in the diagnosis of thyrotoxicosis. There is no doubt that the serum protein-bound iodine is of much greater value for the diagnosis of thyrotoxicosis than is the BMR. Normal serum protein-bound iodine values appear less frequently than do normal basal metabolic rates. For example, in the group of thyrotoxic patients in whom the diagnosis could not be made clinically at the time of study, the serum protein-bound iodine was elevated in 86 per cent of the cases while the BMR was elevated in only 51 per cent of the patients. Furthermore, elevated serum protein-bound iodine values occur more rarely in euthyroid patients

Table 44. The results of the basal metabolic rate, the serum protein-bound iodi

Diagnosis	Number of patients	Basal metabolic rate					Serum protein-bound iodine				
		$< -3\sigma$	-3σ to $< -2\sigma$	-2σ to $+2\sigma$	$> +2\sigma$ to $+3\sigma$	$> +3\sigma$	$< -3\sigma$	-3σ to $< -2\sigma$	-2σ to $+2\sigma$	$> +2\sigma$ to 3σ	$> +$
			Normal range -20 to $+20$ per cent					Normal range 2.7—7.5 μg per cent			
Hyperthyroid:											
Thyrotoxicosis without diagnostic problems	94					**94**					**57**
Thyrotoxicosis with diagnostic problems	77 [1]			20	18	**39**			5	3	**48**
Thyrotoxicosis factitia	3					**3**					**3**
Euthyroid:											
Nontoxic goiter without diagnostic problems	41	**1**	4	31	1						
Nontoxic goiter with diagnostic problems	39 [2]		1	20	6	**10**		2	23	1	**3**
Carcinoma of the thyroid	21 [3]		4	10	1	**2**	**1**		7		
Chronic thyroiditis	11	**2**	1	5		**2**	**1**		3		
Renal disease	10	**2**	2	2			**4**		4		
Diseases simulating thyrotoxicosis:											
Cardiovascular diseases	20			7	5	**6**		2	13		**1**
Anxiety neurosis	22		1	18	2	**1**			13	2	
Diseases of the blood and reticuloendothelial system	10		1	2	1	**4**			2		
Hyperophthalmopathic Graves' disease	4			4					3		
Unilateral exophthalmos	2			2							
Nontoxic goiter without extrathyroid diseases	7			4	1	**2**		1	4		
Miscellaneous diseases	12			5	1	**6**		1	8		**2**
Hypothyroid:											
Myxedema	26	**22**	2	1			**19**	2	1		
Hypothyroidism due to thiocyanate	2 [4]			2				2			

[1] Four patients not included in this table because of recent cholecystograms (see p. 63).

[2] These patients also listed under the heading of "diseases simulating thyrotoxicosis."

[3] Four patients not included in this table for various reasons as indicated on p. 74.

the urinary excretion of I^{131} in patients with various states of thyroid function.

48 hour excretion of I^{131}					0—24 hour excretion of I^{131}					24—48 hour excretion of I^{131}				
-3σ	-3σ to $<-2\sigma$	-2σ to $+2\sigma$	$>+2\sigma$ to $+3\sigma$	$>+3\sigma$	$<-3\sigma$	-3σ to $<-2\sigma$	-2σ to $+2\sigma$	$>+2\sigma$ to $+3\sigma$	$>+3\sigma$	-3σ to $<-2\sigma$	-2σ to $+2\sigma$	$>+2\sigma$ to $+3\sigma$	$>+3\sigma$
	Normal range 44.0—87.8 per cent					Normal range 39.9—81.3 per cent				Normal range 0—11.6 per cent			
94					94					24	70		
71	1	3			72	2	3			24	51		
				3					3		2	1	
	4	21	2	2	1	1	33	1	3	1	23	2	1
	1	34	2	2		1	33	2	1	2	29	4	2
	1	17		2		2	13	1	2	2	14	1	
		7	2	2		1	7	1	2		7	1	3
8	2				10						6	2	2
	1	18		1		3	16				12	4	3
	2	17	1	2		2	17	1	2		19	3	
	1	9				1	8				9		
		3	1				3		1		4		
		2					2				2		
	1	6				1	6			2	4		1
1		10	1		1		10	1			10	1	1
		9	5	12	2	1	21	1	1				26
2					1						1		

[4] The results of the tests will depend upon the length of time between discontinuation of thiocyanate and performance of the tests. A more thorough presentation is found in Table 24 (p. 83).

than do elevated basal metabolic rates. Or in other words, the overlapping of values between euthyroid and hyperthyroid patients is much less for the serum protein-bound iodine than it is for the basal metabolic rate.

The serum protein-bound iodine was less than normal in 19 of 22 patients with myxedema. Subnormal values were also observed in certain clinically euthyroid patients with carcinoma of the thyroid, chronic thyroiditis, and kidney diseases. It is probable that the decreased serum protein-bound iodine in such patients is a sign of incipient thyroid hypofunction. The results obtained in the present study are in good agreement with the observations of previous investigators (Salter, Bassett, and Sappington, 1941; Winkler, Riggs, and Man, 1945; Riggs, 1947; Winkler, 1947).

The serum cholesterol was determined in a considerable number of patients. The results are not included in Table 44, as it has been clearly demonstrated (pp. 59 and 63) that the serum cholesterol is of no value for the diagnosis of thyrotoxicosis. A definitely decreased serum cholesterol which would support the diagnosis of thyrotoxicosis occurred in only one of 122 cases of thyrotoxicosis. In myxedema elevated serum cholesterols were observed rather frequently and may be used as an adjunct in the diagnosis.

In considering the 48-hour urinary excretion of I^{131}, determined from two 24-hour specimens, it is clear that it offers a very dependable method for the diagnosis of thyrotoxicosis. The excretion was invariably less than normal in patients with clinically apparent thyrotoxicosis (Table 44). In thyrotoxic patients who presented diagnostic problems the 48-hour urinary excretion of I^{131} was less than normal in 71 of 75 cases or in 95 per cent. The incidence of failures probably represents a maximum figure, as it was obtained in a group of patients presenting some of the most difficult diagnostic problems that arise in thyrotoxicosis. In unselected patients with thyrotoxicosis the incidence of normal excretion values for I^{131} would certainly have been lower. In the present study the urinary excretion of I^{131} was less than normal in 98 per cent of all patients with endogenous thyrotoxicosis. In patients with thyrotoxicosis factitia the urinary excretion of I^{131} was *higher* than normal, which was of particular diagnostic value as the BMR and the PBI do not differentiate between endogenous and exogenous thyrotoxicosis.

In the various diseases that may simulate thyrotoxicosis the urinary excretion of I^{131} was never less than normal except in one patient. The low excretion in this patient was due to renal impairment, and it could be ascertained from the excretion pattern that the low excretion of I^{131} was not due to thyroid hyperfunction (compare with the discussion of results in kidney diseases).

In no patient with nontoxic goiter, carcinoma of the thyroid, or chronic thyroiditis was the urinary excretion of I^{131} less than normal. It should be observed that the excretion of I^{131} was never below normal even in patients with large colloid goiters.

In a few patients with euthyroidism the urinary excretion of I^{131} was higher than normal. It is not clear how these findings should be interpreted. In several patients

the high excretion was probably due to early hypothyroidism that was not yet recognizable clinically. There may also have been some ingestion of iodine in an unrecognized form. However, an abnormally high excretion of I^{131} in euthyroid patients occurs too rarely to be of practical significance.

In myxedema the urinary excretion of I^{131} presents a characteristic pattern. The total 48-hour excretion is either normal or increased (Table 44), but the 24 -48 hour excretion is invariably higher than normal. In every patient with myxedema the 24—48 hour excretion was more than 15 per cent of the administered dose. However, this characteristically high excretion during the second day is not pathognomonic of myxedema as it may appear in other diseases such as renal disease and cardiovascular disease. To what extent the urinary excretion of I^{131} can be used for diagnostic purposes in myxedema cannot be judged without further studies.

The urinary excretion of I^{131} is not only dependent upon the state of thyroid function but also upon the state of renal function. In renal disease the total 48-hour excretion may be normal or decreased (Table 44). This decreased excretion may at first appear to be a serious limitation to the use of the excretion of I^{131} for the diagnosis of thyrotoxicosis. However, the association of thyrotoxicosis and renal disease is too rare to be of clinical importance. In the present study there was only one patient in whom probable thyrotoxicosis was associated with renal disease. Furthermore, in several patients with kidney disease it was clear that the low 48-hour excretion was not due to thyroid hyperfunction because of the high excretion during the 24—48 hour period. This was true, for example, in the single case in whom a disease simulating thyrotoxicosis was combined with renal impairment. There are good reasons for assuming that the renal damage has to be rather severe before the radioactive iodine tolerance test is seriously affected. For example, in patients with hypertensive cardiovascular disease the 48-hour excretion of I^{131} was never less than normal. It must be stated, however, that a low excretion of I^{131} is an unreliable indication of thyrotoxicosis in the presence of renal disease. It is probable that the interference of kidney disease can be avoided by the more complicated comparison of the rate of excretion of I^{131} with the total excretion. Further studies concerning this problem are necessary. It should also be remembered that renal disease never simulates thyrotoxicosis clinically.

A low excretion of I^{131} may also occur for a short period of time after discontinuing a prolonged course of such drugs as thiocyanate and other goitrogens. However, such a situation appears too rarely to detract from the diagnostic value of the radioactive iodine tolerance test.

With these exceptions a low excretion of I^{131} *seems to be specific for thyrotoxicosis.*

It is of interest to compare the results of the present investigation with previous studies of the urinary excretion of radioactive iodine in thyrotoxicosis. Most of the earlier studies were made in patients with clear-cut thyrotoxicosis and their diagnostic value therefore cannot be judged. However, McArthur *et al.* (1948) and Skanse (1948 a) have illustrated the diagnostic possibilities offered by the uri-

nary excretion of radioactive iodine. In the study of McArthur *et al.* six of 22 thyrotoxic patients gave values within the range observed in nonthyrotoxic patients. This marked overlapping was at least partly due to the very heterogeneous composition of their control group. In the present study the overlapping between thyrotoxic patients and normal subjects amounted to five per cent in the group of thyrotoxic patients with diagnostic problems and to two per cent for all patients with thyrotoxicosis. Werner, Quimby, and Schmidt (1948) considered the urinary excretion of I^{131} of diagnostic help in thyrotoxicosis, but it is difficult to evaluate their results as most of the tests apparently were carried out in patients with unquestioned thyrotoxicosis.

The results of the present study show that the urinary excretion of I^{131} is a far better diagnostic test than are iodine tolerance tests based on chemical methods. When the urinary excretion of iodine was determined by chemical methods, a high degree of overlapping was observed among patients with various states of thyroid function (see Table 3, p. 16). The best results of iodine tolerance tests with chemical methods are those of Soisalo (1949) where the disappearance rate of iodine from the blood was determined. However, with the present radioactive iodine tolerance test a more distinct separation can be made between patients with euthyroidism and with hyperthyroidism.

The urinary excretion of I^{131} is definitely a more sensitive test than is the BMR. While in thyrotoxic patients with diagnostic problems[1] the BMR indicated thyrotoxicosis in 51 per cent, the excretion of I^{131} was correct in 95 per cent of the patients. The specificity of the I^{131}-test is also greater than that of the BMR.

It is more difficult to judge whether the urinary excretion of I^{131} or the serum protein-bound iodine provides the better test for the diagnosis of thyrotoxicosis. In the present group of thyrotoxic patients with diagnostic problems the serum protein-bound iodine indicated thyrotoxicosis in 86 per cent, while the urinary excretion of I^{131} was positive in 95 per cent of the cases. Thus, it is possible that the urinary excretion of I^{131} is slightly more sensitive in detecting thyroid hyperfunction than is the serum protein-bound iodine. The specificity of the two tests seems to be about the same. The serum protein-bound iodine may occasionally be elevated in euthyroid patients. The urinary excretion of I^{131} may be less than normal in patients with kidney diseases and in patients with hyperplastic goiters produced by the prolonged administration of goitrogens. However, in these two latter types of diseases the symptoms and signs do not cause diagnostic confusion in regard to thyrotoxicosis. The urinary excretion of I^{131} has an advantage over the serum protein-bound iodine in that it differentiates between endogenous thyrotoxicosis and thyrotoxicosis produced by an excessive intake of thyroid. It may be of interest to point out that in the present study there appeared no case of thyrotoxicosis in whom both the radioactive iodine test and the serum protein-bound iodine failed to indicate thyrotoxicosis.

[1] Of course, patients with normal BMR's were referred to that group.

Table 45. **Coefficient of correlation, r, and its standard error, $\varepsilon(r)$, for different tests.**

Correlation between	Number	$r \pm \varepsilon(r)$
BMR—PBI	111	$+0.64 \pm 0.06$
BMR—I^{131}-excretion	169	-0.46 ± 0.06
PBI—I^{131}-excretion	111	-0.54 ± 0.07

The results of the urinary excretion of I^{131} so far discussed are based on the 48-hour excretion, determined from two 24-hour specimens. The extended urine collection is a disadvantage for the test. The results, as indicated in Table 44, demonstrate that the 24-hour excretion of I^{131} gives almost as good diagnostic results. The most apparent disadvantage with a single 24-hour collection is the fact that there will be no possibility of analyzing whether a low excretion is due to thyroid hyperfunction or renal impairment. However, in the absence of renal disease the 24-hour excretion of I^{131} is a dependable test in the diagnosis of thyrotoxicosis. Another disadvantage with a test based on the 24-hour excretion of I^{131} is that hypothyroidism cannot be detected with a single 24-hour specimen.

The radioactive iodine tolerance test can be further simplified if direct measurements of the uptake of I^{131} by the thyroid are substituted for the determination of the urinary excretion. The results obtained in the present study indicate that this may be justified.

The previous discussion has shown that the BMR, the serum protein-bound iodine, and the I^{131}-excretion do not invariably run parallel to each other in thyrotoxicosis. A more complete analysis of the relation among the three tests in thyrotoxic patients is shown in Table 45, which gives the total correlations observed between the results of the three tests. The scatter diagrams (Figs. 20, 21, and 22) present the results graphically.

A significant correlation is observed between the results of the three tests. It is only moderately high, however. This is partly due to methodological inaccuracies which decrease the real correlations. Primarily, however, it is due to the fact that the tests measure different aspects of thyroid function. The BMR may be considered to be an index of the impact of thyroid hormone on the body cells. The serum protein-bound iodine is an index of the hormone level proper. The excretion of I^{131} reflects the gland's avidity for iodine.

The fact that the tests measure different functions is nicely illustrated by the partial correlation coefficients shown in Table 46. These give the correlation between any two tests as it would have been obtained if it had been possible to select the patients in such a manner that the result of the third test was the same in all of them.

The highest correlations, as expected, are observed between those pairs of tests which measure physiologically most closely connected functions. Thus, the PBI

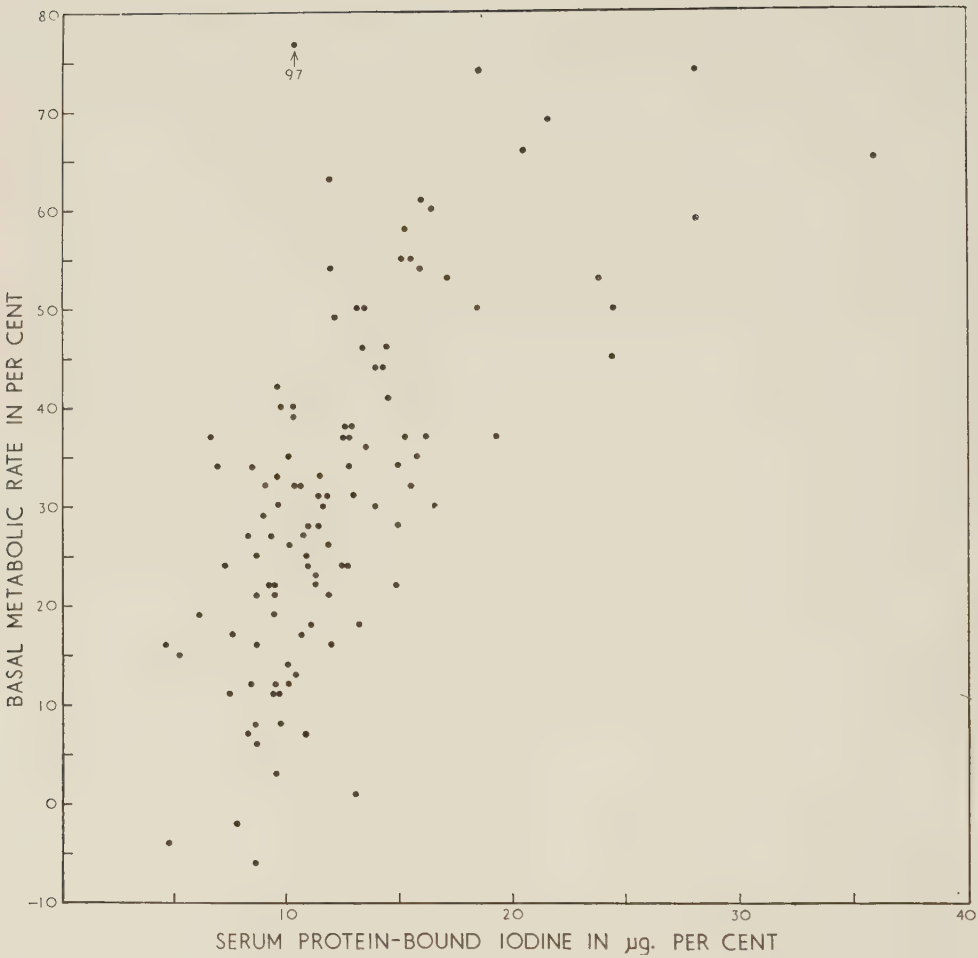

Fig. 20. Diagram showing the relation of the basal metabolic rate to the serum protein-bound iodine in thyrotoxic patients.

and the BMR, measuring the hormonal level and the effect of the hormone, show a rather good correlation. The I^{131}-excretion and the PBI show a weaker correlation. Finally, the I^{131}-excretion and the BMR, which measure functions which are not directly related, show only an insignificant correlation.

Table 46. **Partial correlations calculated from the total correlation coefficients.**

Correlation between	Test held constant statistically	Correlation coefficient
BMR—PBI	I^{131}-excretion	+0.52
BMR—I^{131}-excretion	PBI	−0.18
PBI—I^{131}-excretion	BMR	−0.36

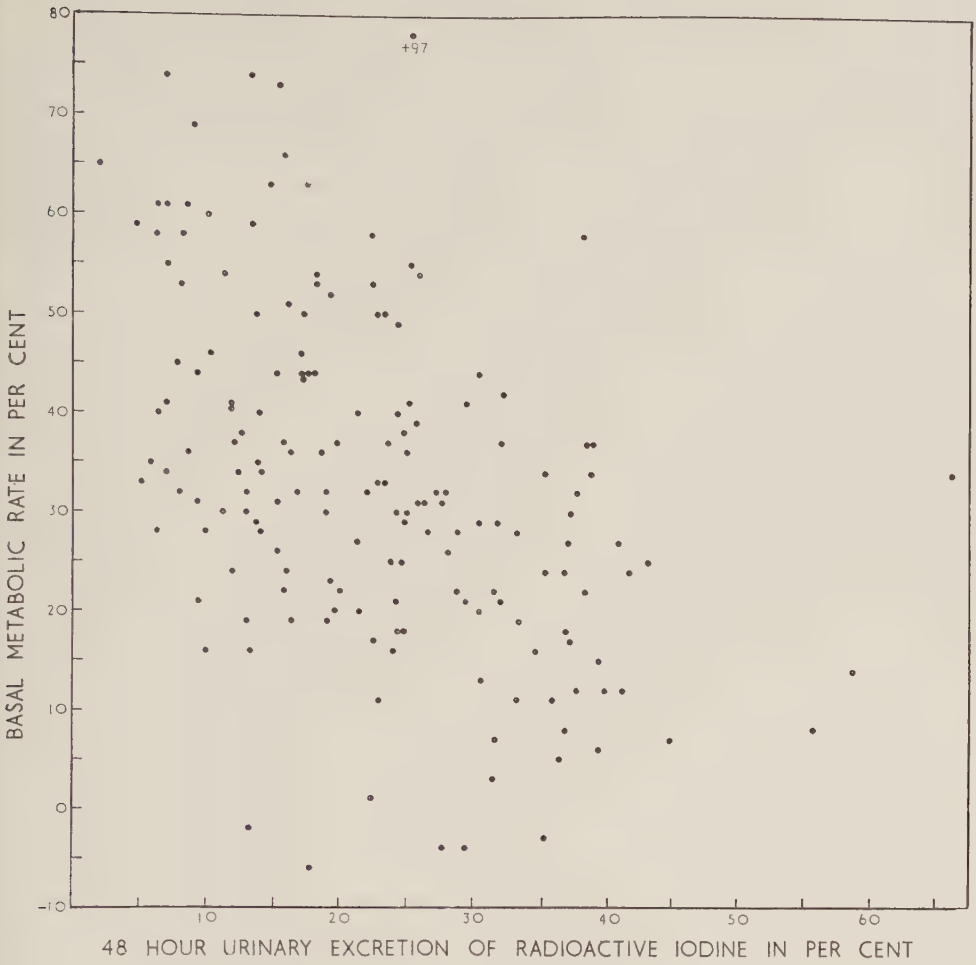

Fig. 21. Diagram showing the relation of the urinary excretion of I^{131} to the basal metabolic rate in thyrotoxic patients.

That the correlation between the serum protein-bound iodine and the BMR is not higgher may be due to individual variations in the sensitivity of the body cells to thyroid hormone. Furthermore, the functional state of the thyroid represents only one of the factors that determine the basal oxygen consumption.

The rather low correlation between the PBI and the excretion of I^{131} may seem surprising. One would have expected a higher correlation inasmuch as the thyroid's avidity for iodine must be related to the output of thyroid hormone. On the other hand, the degree of saturation of the body with iodine and possibly the functional state of the kidneys with respect to iodine excretion in thyrotoxic patients are other factors which may influence the amount of I^{131} excreted in any single case and thus lower the correlation.

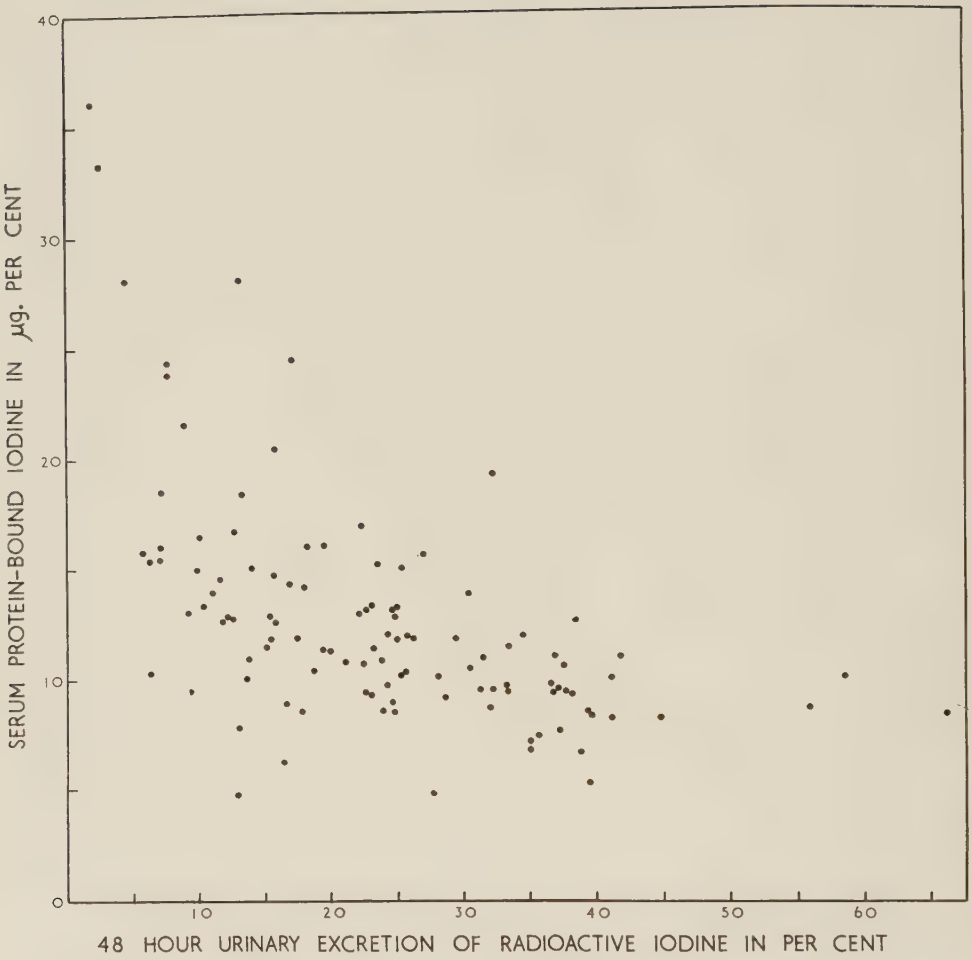

Fig. 22. Diagram showing the relation of the urinary excretion of I^{131} to the serum protein-bound iodine in thyrotoxic patients.

A further fact that probably tends to reduce the correlations below the real values is that the absolute values of the tests are less important from the physiological point of view than are the deviations from the normal value for any given individual. Finally, the fact that some of the functional relationships may not be linear will lower the correlation coefficients when they are calculated as being linear.

On the other hand the total correlation between the BMR and the I^{131}-excretion could not be expected to be high, because at a constant PBI the excretion of I^{131} *per se* has little or no influence on the BMR. This latter fact is indicated by the very low partial correlation coefficient between the BMR and the I^{131}-excretion.

The basal metabolic rate has been the classical laboratory test in thyrotoxicosis. It is true that the BMR is elevated in the majority of patients with thyrotoxicosis.

However, elevated basal metabolic rates occur particularly in patients in whom the diagnosis of thyrotoxicosis can be made on purely clinical grounds. The present study has demonstrated that the BMR fails to indicate thyrotoxicosis in a high percentage of patients in whom a laboratory test is especially needed. Furthermore, the BMR cannot be relied upon in patients with complicating diseases that in themselves are capable of raising the BMR. Under such circumstances the serum protein-bound iodine and the radioactive iodine tolerance test can be used more successfully for the diagnosis. If one could have all three tests, a more complete picture of the disturbed thyroid function would be obtained than with one or two tests. However, this is usually impossible in clinical work. If only one test should be used in addition to the BMR, the problem arises which test should be recommended. The determination of the serum protein-bound iodine involves a complicated and time-consuming procedure that requires the most careful analytical technique. Satisfactory results have been obtained in only a few highly specialized laboratories. The determination of the serum protein-bound iodine was suggested many years ago. The fact that this test so far has found comparatively little clinical use may be attributed to the difficulties involved in obtaining accurate analyses.

The determination of the urinary excretion of I^{131} is a rather simple and precise test for the diagnosis of thyroid hyperfunction. The analyses for radioactive iodine are accurate, rapid, and reliable. The collection of complete urine specimens may involve a problem particularly for out-patients, but if the test is limited to 24 hours the urine collection is no serious drawback. The radioactive iodine tolerance test is even simpler when the uptake of radioactive iodine by the thyroid is determined. The latter procedure is, however, somewhat less sensitive than is the determination of the urinary excretion. So far the use of radioactive iodine tolerance tests have been limited by the fact that radioactive iodine has not been available in all places. There are good reasons to assume that this limitation will disappear. The present study has demonstrated that the radioactive iodine tolerance test can be advantageously used in the diagnosis of thyrotoxicosis. It may be suggested for more common clinical use.

Chapter XII

SUMMARY

The recognition of thyrotoxicosis in its classical form is not difficult. Laboratory tests are often unnecessary except in following the course of disease. There are many cases, however, in which the clinical picture is equivocal or confusing and which require the help of laboratory tests in establishing the diagnosis. Of all tests devised for this purpose the basal metabolic rate is most widely used, but a review of the literature shows that it is unreliable in just those borderline and atypical cases in which the results of the test are most important. The serum protein-bound iodine has given good results in a few studies, but it is impractical for widespread use. In the present study an iodine tolerance test using radioactive iodine has been developed in an attempt to make a reliable and practical test available for use in the clinic. The test is an indirect measure of the avidity of the thyroid for iodine; that is, the administered iodine is, presumably, either taken up by the thyroid or excreted in the urine. This is supported by the observation that in totally thyroidectomized patients essentially all radioactive iodine was excreted in the urine (p. 54).

The test has been standardized on the basis of the amount of I^{131} excreted in the urine in two 24-hour periods after the oral administration of 100 μg. of inactive iodine labelled with 100 μc. of I^{131}. The results obtained have been compared throughout with the diagnosis established on clinical grounds and with the behavior of the BMR, the serum protein-bound iodine, and the serum cholesterol. (The last proves to be of negligible diagnostic value in thyrotoxicosis.) The standardization of such a test requires a careful control of the variables involved in the actual performance of the test, and subsequently an exploration of the values obtained in a wide spectrum of thyroid disorders, in diseases simulating these disorders, and in normal controls.

The chief variables in the performance of the test are the size of the dose of the inactive (carrier) iodine and the size of the dose of radioactive iodine. It was found that the test is not influenced by the amount of carrier iodine when 100 μg. or less are used, except that unexpected losses of I^{131} may occur when no carrier is added (pp. 34—38). Similarly, the amount of I^{131} may vary from a tracer dose of 100 μc. or less to a therapeutic dose of 6000—14,000 μc. without affecting the percentage excretion (p. 34). However, it is necessary to know in absolute units how much

radioactive material is given, both for the obvious methodological advantages and as an essential safety precaution. There has been no evidence that 100 μc. of I^{131} exercises any untoward radiation effect in humans. For the standardization in absolute units (curies) a method is presented which is based on the comparison of the gamma radiation of I^{131} with that of radium by Geiger-Müller counters that are calibrated by coincidence measurements (pp. 28—33). An accurate technique has been described for the measurement of radioactive iodine in the urine (pp. 38—42); the overall variability in carrying out the test with these methods is small as evidenced by a high repeat reliability (pp. 43—44).

The clinical material investigated by means of this test is composed of 110 normal controls and 385 patients (with various diseases, mostly thyroid in origin) of whom 172 were in a euthyroid state, 187 in a hyperthyroid state, and 26 in a hypothyroid state. There was a large proportion of atypical and confusing cases.

In normal subjects it was found that 65.9 ± 0.7 per cent of the administered I^{131} was excreted in the urine in 48 hours. Of the amount excreted roughly 90 per cent is excreted in the first 24 hours. No significant difference was observed between men and women or among various age groups. The limits of normalcy were arbitrarily placed at three times the standard deviation above and below the mean value of 65.9 per cent. The normal range of excretion thus can be said to lie between 44.0 and 87.8 per cent of the administered I^{131}. This range includes 99.7 per cent of normal subjects and values outside it are almost certainly abnormal.

In patients with thyroid disease the test gave a very reliable indication of the state of thyroid function. Ninety-eight per cent of all patients with thyrotoxicosis had an abnormally low excretion of I^{131}. Thus, only two per cent of the thyrotoxic patients, many of whom were atypical cases, would have been wrongly diagnosed with the radioactive iodine excretion test used alone, whereas 22 per cent would have been missed with the BMR and seven per cent with the serum protein-bound iodine at the time of study.

Euthyroid patients with thyroid disease (nontoxic goiter, carcinoma of the thyroid, chronic thyroiditis) in no instance had excretion values less than normal. In a few patients the excretion was higher than normal. By comparison the BMR was elevated in 14 per cent of the cases, primarily due to the presence of extrathyroidal diseases.

In patients with myxedema the total excretion in 48 hours was either normal or increased, but there was invariably a delay in excretion so that the amount excreted in 24—48 hours was conspicuously increased.

It is thus clear that the state of thyroid function is well reflected by the test. However, the results are influenced by certain other factors. There are those which disturb iodine metabolism, principally the administration of drugs containing iodine (e.g. contrast media, iodides), antithyroid drugs, or desiccated thyroid. All these increase the excretion of I^{131}. There are also factors which tend to decrease iodine excretion, notably kidney disease, which may result in values below the normal

range. Moderately severe congestive heart failure was found not to invalidate the results of the test. An extensive survey has been presented of the diagnostic value of the test in thyrotoxicosis with a number of case reports to illustrate the problems in which it is of help. The test is of particular value when the clinical picture is obscure, whether it is unusually mild, atypical, or complicated by other diseases. This is especially true if the BMR in these situations is normal or may have been elevated by the complicating disease.

The test is also an effective aid in ruling out the diagnosis of thyrotoxicosis in patients with diseases simulating it. Any patient with an elevated BMR, especially in combination with a goiter, is suspect of thyrotoxicosis. This is particularly true when the underlying disease mimics thyrotoxicosis in other ways as well, as may occur in cardiovascular disease, anxiety neurosis, and certain constitutional illnesses.

There are occasional cases of factitious thyrotoxicosis induced by excessive ingestion of thyroid hormone. In such cases the clinical picture, the BMR, and the serum protein-bound iodine all suggest a hyperfunctioning thyroid gland. The radioactive iodine tolerance test, however, clearly indicates the artificial nature of the disease, as practically all of the I^{131} is excreted in the urine.

A technique has been developed for the quantitative *in vivo* determination of the collection of I^{131} by the thyroid by means of direct radiation measurements over the gland. These direct measurements showed a very high correlation with the urinary excretion of I^{131}, and it may be possible to substitute this simpler measurement technique for the excretion test. However, as a diagnostic method for detecting thyrotoxicosis the tolerance test based on *in vivo* measurements is somewhat less sensitive than is the urinary excretion test.

In conclusion, it may be stated that the radioactive iodine excretion test as presented here is an effective and reliable aid in the diagnosis of thyroid disease, particularly in the diagnosis of thyrotoxicosis. It is far superior to the determination of the basal metabolic rate and it is better suited than the determination of the serum protein-bound iodine to general clinical use.

APPENDIX

The case numbers correspond to the following numbers in the hospital records:

1	505 014	38	608 487	75	597 500	112	503 424	149	590 119
2	571 526	39	545 996	76	610 635	113	110 950	150	531 842
3	614 127	40	152 677	77	492 058	114	45 437	151	285 835
4	544 906	41	510 595	78	577 538	115	590 045	152	541 720
5	598 562	42	557 306	79	610 847	116	—	153	42 039
6	386 747	43	546 461	80	437 125	117	358 204	154	476 232
7	225 980	44	583 083	81	85 868	118	551 728	155	624 162
8	192 618	45	510 792	82	596 085	119	284 091	156	361 085
9	447 449	46	563 059	83	553 085	120	444 468	157	419 349
10	304 089	47	576 215	84	530 285	121	609 540	158	479 083
11	551 817	48	459 451	85	601 877	122	234 216	159	9 911
12	422 567	49	586 351	86	570 125	123	619 095	160	583 663
13	594 681	50	616 882	87	592 573	124	605 322	161	364 311
14	589 779	51	610 833	88	578 868	125	616 211	162	327 474
15	527 838	52	313 797	89	568 466	126	520 704	163	5 495
16	569 008	53	582 470	90	333 006	127	601 801	164	383 094
17	572 445	54	101 872	91	583 567	128	308 122	165	548 981
18	615 641	55	619 090	92	556 106	129	595 937	166	555 538
19	624 161	56	569 942	93	586 905	130	436 878	167	560 721
20	533 628	57	604 233	94	542 477	131	45 926	168	279 930
21	576 028	58	369 099	95	550 458	132	620 912	169	65 031
22	602 063	59	—	96	569 019	133	552 197	170	577 406
23	561 373	60	613 765	97	605 449	134	493 176	171	496 977
24	561 450	61	594 175	98	543 733	135	534 339	172	75 570
25	145 390	62	602 774	99	574 853	136	609 169	173	622 847
26	581 513	63	552 340	100	—	137	577 513	174	418 230
27	600 444	64	314 599	101	575 303	138	107 217	175	286 296
28	578 600	65	519 162	102	616 886	139	549 244	176	552 354
29	—	66	551 723	103	530 221	140	602 114	177	349 932
30	581 124	67	525 625	104	551 711	141	100 743	178	612 764
31	562 220	68	560 084	105	341 470	142	458 712	179	568 555
32	406 057	69	590 280	106	—	143	32 121	180	549 248
33	605 752	70	—	107	560 922	144	600 389	181	446 483
34	541 122	71	600 381	108	108 717	145	508 594	182	569 010
35	487 955	72	481 818	109	563 794	146	230 143	183	616 977
36	580 934	73	595 019	110	342 262	147	605 195	184	610 276
37	—	74	597 622	111	219 202	148	566 426	185	10 088

186	31 359	226	596 938	266	608 703	306	580 910	346	592 952
187	571 626	227	566 377	267	595 345	307	267 629	347	4 017
188	—	228	615 719	268	564 837	308	368 305	348	604 904
189	613 500	229	437 992	269	539 626	309	107 470	349	585 078
190	153 678	230	606 940	270	575 018	310	551 367	350	533 936
191	591 236	231	560 647	271	493 834	311	15 160	351	570 522
192	530 417	232	410 281	272	94 788	312	45 127	352	615 253
193	619 629	233	603 578	273	569 120	313	568 954	353	522 488
194	609 529	234	588 749	274	513 841	314	264 633	354	—
195	522 133	235	36 095	275	537 907	315	349 245	355	579 877
196	12 143	236	574 380	276	576 603	316	576 013	356	580 654
197	607 941	237	474 424	277	599 815	317	582 016	357	521 586
198	552 626	238	546 178	278	528 012	318	275 737	358	437 934
199	546 642	239	600 658	279	587 606	319	557 322	359	467 974
200	619 282	240	590 752	280	618 329	320	538 688	360	603 769
201	222 071	241	420 085	281	84 196	321	618 973	361	606 636
202	508 660	242	—	282	624 607	322	588 507	362	155 147
203	577 911	243	620 552	283	608 691	323	553 750	363	600 401
204	510 174	244	619 094	284	558 898	324	457 725	364	—
205	593 002	245	325 810	285	561 254	325	617 125	365	603 118
206	554 017	246	581 677	286	596 961	326	287 346	366	557 300
207	59 013	247	555 669	287	577 751	327	614 413	367	80 656
208	55 831	248	327 906	288	542 880	328	583 133	368	169 823
209	142 712	249	597 923	289	481 114	329	611 818	369	47 565
210	557 745	250	627 626	290	365 865	330	113 448	370	—
211	566 571	251	163 072	291	590 506	331	420 648	371	488 442
212	85 306	252	586 857	292	548 704	332	436 315	372	512 433
213	617 949	253	612 883	293	606 668	333	—	373	590 714
214	578 373	254	376 321	294	594 934	334	606 999	374	601 039
215	477 592	255	154 593	295	479 007	335	560 495	375	603 693
216	561 960	256	583 096	296	503 075	336	166 435	376	522 969
217	346 506	257	574 337	297	610 881	337	40 762	377	482 716
218	480 671	258	603 949	298	608 313	338	602 735	378	522 595
219	563 486	259	595 302	299	318 733	339	8 997	379	520 850
220	566 101	260	431 385	300	515 625	340	542 502	380	565 200
221	562 281	261	515 455	301	531 285	341	603 117	381	302 523
222	88 441	262	620 860	302	242 350	342	597 264	382	568 066
223	561 522	263	521 579	303	306 705	343	591 788	383	395 641
224	571 601	264	611 385	304	587 183	344	590 030	384	559 680
225	576 070	265	600 898	305	593 494	345	588 865	385	537 925

Patients without hospital numbers were referred for study by private doctors.

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